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CONTRIBUTION TO THE CHEMISTRY OF THE PITUITARY PRESSOR COMPOUNDS.

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After having discovered the pressor action of the extracts of the adrenal glands, Oliver and Schaefer [1] studied the action of those made from other ductless glands. They found that aqueous or glycerine extracts of sheep pituitaries, on intravenous injection into certain animals, caused a persistent rise in blood-pressure, usually, but not always, associated with a slowed heart-rate. This rise occurred even in animals with the medulla destroyed, and perfusion experiments proved the action to be mainly peripheral. An increase in the force of the heart action is partly responsible for this rise, as extracts of pituitary glands act directly on the muscle-fibres of the vessels and heart. The pressor action is especially marked in cases of artificially lowered blood-pressure.

The few experiments which Szymonowicz [2] made suggested that extracts of this organ caused a fall in blood-pressure with a rapid heart-beat, the opposite condition to what Oliver and Schaefer found. Silvestrini [3] merely noted a fall in blood-pressure, and this seemed to be the characteristic reaction. According to von Cyon, there are two compounds: one which slows and strengthens the

[1] Oliver, G., and Schaefer, E. A., "On the Physiological Action of Extracts of Pituitary Body," *Jour. of Physiology*, vol. 18, p. 277 (1895).

[2] Szymonowicz, L., "Die Function der Nebennieren," *Archiv. f. Physiol.*, vol. 64, p. 131 (1896).

[3] Silvestrini, R., "Sull' azione dell' estratto aquoso del lobo posteriore dell' ipofisi sulla pressione sanguinea," *Revista critica di clin. med.*, No. 28, 1905, seen only in reference.

heart, while the other causes a rise in blood-pressure through inhibition of the depressor nerve.[4]

Howell [5] traced the pressor action of the pituitary exclusively to the infundibular portion, and found that, if the injection of extracts of this portion were repeated rapidly, the second injection caused no rise in blood-pressure and produced no cardiac inhibition. He also found that extracts of the anterior lobe usually induced no effect, either on the blood-pressure or on the heart-rate. If the vagi were intact, as in Oliver and Schaefer's original experiments, extracts of the infundibular lobe caused a rise in blood-pressure with a slow heart-beat, but if the vagi were cut there was a rise in pressure with less slowing than when the vagi were intact, hence the action is partly central. Other workers have found that some of the cardiac slowing is peripheral in origin.[6]

In Howell's experiments both sheep and dog pituitaries were used and were tested on dogs. Schaefer and Vincent [7] confirmed Howell's conclusions that the pressor principle was confined to the infundibular portion, and the latter workers made the further suggestion that in extracts of this gland there was a depressor compound. They agreed with Howell that a second injection, if given too soon after the first, would cause no immediate rise in blood-pressure, but claimed there might be a delayed rise and that the second injection produced a more marked fall, so that no tolerance to the depressor action was produced. The depressor action still occurred after the use of atropin and was, therefore, not due to cholin. Slowing of the heart was not constant, but when present might be very persistent.

They found that the pressor compound, at least in the form in which it existed in the glands, was insoluble in alcohol or ether, while the depressor body was soluble in absolute alcohol. Schaefer

[4] Cyon, E. v., "Die physiologischen Herzgiften," *Arch. f. ges. Physiol.*, vol. 73, p. 339 (1898).

[5] Howell, W. H., "Physiological Effects of Extracts of the Hypophysis," *Jour. Exper. Med.*, vol. 3, p. 245 (1898).

[6] Hebdom, K., "Ueber die Einwirkung verschiedener Stoffe auf das isolierter Säugetierherz," *Skan. Arch. f. Physiol.*, vol. 8, p. 147 (1898); Cleghorn, A., "Action of Animal Extracts . . . on Mammalian Heart Muscle," *Amer. Jour. Physiol.*, vol. 2, p. 273 (1899).

[7] Schaefer, E., and Vincent, S., "Physiological Effects of Extracts of the Pituitary Body," *Jour. Physiol.*, vol. 25, p. 87 (1899).

and Herring [8] found little or no rise in blood-pressure if the pituitary extracts were given animals by mouth, but believed the compound which gave immunity was still absorbed, because the depressor effect of intravenous injections was more marked if given after the oral use of such extracts. They state that a very small dose (1 c.c. of a 1 per cent. extract) does not produce immunity, although the rise in blood-pressure which follows a second injection is less than that which follows the first. In this connection it is interesting to note that Biedl [9] and also Cushing have found that removal of the posterior lobe is borne by dogs apparently with slight danger to life, whereas removal of the anterior lobe will cause death within a few days; also Ott and Scott [10] have found that the injection of extracts of the posterior lobe will cause a diminution in size of the thyreoid gland, but that extracts of the anterior lobe will cause enlargement of this gland.

In Hamburger's experiments extracts of the anterior lobe caused a fall in blood-pressure with weakening of the heart and acceleration of the rate, while a second injection, if given early, produced no effect on the blood-pressure, although if the interval between injections was longer a fall still occurred. At the autopsy of one of Biedl's animals, similarly injected, there was widespread clotting.[11]

The fall from injection of extracts of the anterior lobe is more marked in atropinized animals, but Biedl [12] does not consider the fall produced by extracts of the anterior lobe as characteristic. Hamburger noted that a secondary rise at times followed the depression caused by the injection of extracts of the anterior lobe.[13]

Émile-Weil and Boyé [14] claim there is a further difference between the action of extracts of the anterior and of the posterior

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[8] Shaefer, E., and Herring, P. T., "Action of Pituitary Extracts upon the Kidney," *Philos. Trans. Roy. Soc. London*, Ser. B, vol. 199, p. 1 (1908).

[9] Biedl, A., "Innere Sekretion," vol. 2, p. 116.

[10] Ott, I., and Scott, J. C., "Effect of Animal Extracts and Iodine upon the Volume of the Thyroid Gland," *Therap. Gaz.*, vol. 37, p. 781 (1913).

[11] Biedl, *l. c.*, p. 141.

[12] Biedl, *l. c.*, p. 141.

[13] Hamburger, W. W., "Action of Intravenous Injections of Glandular Extracts," *Amer. Jour. Physiol.*, vol. 11, p. 282 (1904).

[14] Émile-Weil, P., and Boyé, G., "Action différente des lobes hypophysaires sur la coagulation du sang," *Compt. rend. Heb. Soc. de Biol.*, vol. 67, p. 428 (1909).

lobes, in that extracts of the latter favor coagulation of the blood, while those of the former do not.

Paton and Watson [15] have found that extracts of the pituitary gland (pituitrin), when injected intravenously into birds, caused a fall in blood-pressure, and that after repeated injections this depressor action failed to appear, although, at times, such injections caused a rise in blood-pressure. In birds the fall in pressure was due to dilatation of the abdominal vessels, and might be neutralized by more powerful ventricular contraction.

It has been recently shown that the effects of extracts of the pituitary gland depend to some extent upon how rapidly they are injected; thus Miller and Miller [16] state that "if a strong saline extract of the posterior lobe of the hypophysis be injected rapidly a depressor effect only may be obtained, whilst if the injection be made slowly or in a very dilute form, the pressor effect predominates."

On purely histological evidence Herring [17] separated the pituitary gland into an anterior, a posterior, and an intermediary portion, and argued that the pressor principle originated in the pars intermedia. Recently Lewis, Miller and Matthews [18] have found that the more sharply the intermediary portion of the pituitary is removed and extracted, the greater the rise in blood-pressure which results from injection of such extracts, and the less of the pars intermedia is used the less the rise. Biedl claims that the pars intermedia can be removed comparatively easily in thyreoidectomized animals and that the injection of aqueous extracts of this portion of the gland causes a slowed heart with a rise in blood-pressure, while extracts of the pars nervosa, freed from the pars intermedia, are inactive, save in producing a slight fall.

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[15] Paton, D. H., and Watson, A., "Actions of Pituitrin, Adrenalin, and Barium on the Circulation of the Bird," *Jour of Physiol.*, vol. 44, p. 413 (1912).

[16] Miller, J. L., and Miller, E. M., "Effects on Blood-pressure of Organ Extracts," *Jour. of Physiol.*, vol. 43, p. 242 (1911).

[17] Herring, P. T., "Histological Appearances of the Mammalian Pituitary Body," *Quart. Jour. Phys.*, vol. 1, p. 1214 (1908).

[18] Lewis, D., Miller, J. L., and Matthews, S. A., "Effects on Blood-pressure of Various Anatomical Components of the Hypophysis," *Archives of Int. Med.*, vol. 7, p. 785 (1911). See also Schickele, G., "Ueber die Herkunft der blutdrucksteigernden Substanz in der Hypophysis," *Zeits. f. gesam. Med.*, vol. 1, p. 545 (1913).

Lewis, Miller and Matthews believe the pars intermedia to be separated by the hypophyseal cleft into one portion closely connected with the anterior lobe and one with the posterior. This may explain why a rise in pressure may follow the injection of extracts of either lobe. They obtained a rise in pressure more frequently from injections of extracts of the anterior lobe than from those of the posterior. Schaefer and Herring were inclined to the view that the activity of the anterior lobe might really be due to postmortem infiltration.

Lewis, Miller and Matthews found that after removal of the depressor compound, extracts of the pars intermedia caused a rise in blood-pressure without slowing of the pulse-rate. They, like Howell, also noted that extracts of the posterior lobe caused a rise in blood-pressure, which was followed by a fall, and that there was then a return to the higher level. This fall after the primary rise was only seen when extracts of the posterior lobe were used, and they attributed this to a second depressor principle which was insoluble in alcohol.

Osborne and Vincent [19] found that the pituitaries of various teleostean fishes exerted a pressor action, and claimed that the central part of the infundibular portion of the ox pituitary had more pressor activity than the peripheral portion. In a recent comparative study of the pituitary gland Herring sums up the work as follows: "The presence of active physiological principles in the pituitary is associated with a tissue of nervous origin," and "there is reason to believe that the granules are the histological representatives of the active principles, and that they are the products of part of the epithelial lobe—the cells of the pars intermedia—carried to, elaborated in, and stored by, the pars nervosa."

Vincent and Sheen [20] took the position that pressor principles could be found not only in the pituitaries and suprarenals, but in greater or less extent in most tissues, and that boiling the extracts

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[19] Osborne, W. A., and Vincent, S., "Contribution to the Study of the Pituitary Body," *Brit. Med. Jour.* (1900), vol. 1, p. 502.

[20] Vincent, S., and Sheen, W., "Effects of Intravascular Injections of Extracts of Animal Tissues," *Jour. of Physiol.*, vol. 29, p. 242 (1903). See also McCord, C. P., "Investigation of the Depressor Action of Pituitary Extracts, *Archives of Int. Med.*, vol. 8, p. 609 (1911); Berlin, E., "Hemocholin und Neosin," *Zeits. f. Biol.*, vol. 57, p. 1 (1911).

made from these organs usually enhanced the depressor action and masked the pressor effects. Miller and Miller found that, by autoclave treatment, the pressor action of pituitary extracts disappeared, while the depressor persisted.

It has been shown [21] that in cats the injection of extracts of pituitary glands, taken from almost any vertebrate animal, will increase the urinary secretion. This action has been claimed by some [22] to be due to its pressor principle, but there is physiological evidence to show that the diuretic and pressor actions are due to separate constituents. This diuretic action is confined to the posterior lobe, and second injections of such extracts do not produce tolerance to its diuretic effect, but rather increase its action. Extracts of pituitary glands taken from some animals have little or no effect on blood-pressure, yet exert a diuretic action.[23]

It has been found that extracts of pituitary glands exert an action on various organs which are supplied with unstriated muscles, such as the uterus,[24] intestines, bladder, etc. Recently Barger and Dale have shown that various amines will not only produce a rise in blood-pressure, but also affect various organs with unstriated muscles. In this case the action is on the extreme terminals (receptor bodies) of the sympathetic nerves supplying these organs, and these observers have designated this action as "sympathomimetic." In the case of the pituitary extracts the action, at least on the uterus, seems to be different, and is believed by Dale to be on the muscles rather than on the sympathetic nerve-endings. This view is supported by the experiments of Paton and Watson on birds.

The pressor principle and the one which causes uterine contractions may not necessarily be the same, or, at least, all of the uterine

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[21] Schaefer, E. A., and Herring, P. T., "Action of Pituitary Extracts upon the Kidney," *Philos. Trans. Roy. Soc. London*, Ser. B, vol. 199, p. 1 (1908).

[22] Houghton, E. M., and Merrill, C. H., "Diuretic Action of Adrenalin and the Active Principle of the Pituitary Body," *Jour. Amer. Med. Assoc.*, vol. 51, p. 1849 (1908).

[23] Herring, P. T., "Further Observations upon the Comparative Anatomy and Physiology of the Pituitary Body," *Quart. Jour. Exper. Physiol.*, vol. 6, p. 73 (1913).

[24] Bayer, G., and Peter, L., "Zur Kenntniss des Neurochemismus der Hypophyse," *Arch. f. exper. Path.*, vol. 64, p. 204 (1911).

action may not be due to the pressor principle. Engeland and Kutscher [25] have attempted to isolate the compound which causes contractions in the cat uterus. They attributed this action to cholin, as they isolated this base from pituitaries and found that control solutions of cholin caused contractions of the isolated uterus. Gautrelet had previously found cholin in the hypophysis. Engeland and Kutscher believe the pressor principle to be different from the one which acts on the uterus.

Bayer and Peter [26] claim that the pituitary principle which stimulates the autonomic nerve-endings of the intestines resides in the posterior lobe only and is not specific for this organ, and that the portion of the lobe insoluble in alcohol causes inhibition, while the portion soluble in alcohol causes increased activity. On isolated bronchial muscle, extracts of the hypophysis, histamine, and Witte's pepton caused no contraction.[27]

Like the secretion of the ovaries, extracts of the pituitary glands also increase the secretion of the mammary gland.[28] According to Herring,[29] extracts of the pituitary gland of skates produce an increase in mammary secretion, but do not produce a rise in blood-pressure or increase in urinary secretion.

The apparent similarity [30] in some of the actions of pituitary ex-

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[25] Engeland, R., and Kutscher, F., "Ueber einige physiologischen wichtige Substanzen," *Zeits. f. Biol.*, vol. 57, p. 527 (1912); Schickele, G., "Ueber die Herkunft der blutdrucksteigernden Substanz in der Hypophysis," *Zeits. f. d. ges. exp. Med.*, vol. 1, p. 545 (1913); Bell, W. B., "Pituitary Body," *Brit. Med. Jour.* (1900), vol. 2, p. 1609.

[26] Bayer, G., and Peter, L., "Zur Kenntniss des Neurochemismus der Hypophyse," *Archiv. f. exper. Path.*, vol. 64, p. 204 (1911).

[27] Trendelenburg, P., "Physiologische und pharmakologische Untersuchungen an der isolierten bronchial Muskulatur," *Archiv. f. exper. Path.*, vol. 69, p. 106 (1912).

[28] Ott, I., and Scott, J. C., *Proc. Soc. Exper. Biol.*, vol. 1, p. 1911); Schaefer, E. A., "On the Effect of the Pituitary and Corpus Luteum Extracts on the Mammary Secretion in the Human Subject," *Quart. Jour. Exper. Physiol.*, vol. 6, p. 17 (1913); Gavin, W., "On the Effects of Administration of Extracts of Pituitary Body and Corpus Luteum to Milch Cows," *ibid.*, p. 13.

[29] Herring. P. T., "Contribution to the Comparative Physiology of the Pituitary Body," *Quart. Jour. Physiol.*, vol. 1, p. 261 (1908).

[30] Claude, H., and Baudoin, A., "Sur les effets de certains extraits hypophysaires," *Comp. rend. Acad. des Sci. Paris*, vol. 153, p. 1513 (1911); v. Frankl-Hochwart, L., and Fröhlich, A., "Zur Kenntniss der Wirkung des Hypophysins," *Archiv. f. exper. Path.*, vol. 63, p. 347 (1910).

tracts with those of epinephrin suggested the identity, or at least a close chemical relationship of the pressor principle of the pituitary with that of the adrenal glands, but Allers and Houssay [31] proved that the chemical reactions of pituitary pressor extracts were different from those of epinephrin, and the method used for isolating epinephrin from the suprarenal glands failed to yield this compound when tried on pituitary extracts. Meyers [32] has shown that, while repeated intravenous injections of epinephrin produced arterial degeneration in rabbits, pituitrin caused almost no vascular changes; and Cramer [33] has claimed that, while epinephrin when mixed with formaldehyde rapidly lost its pressor activity, Pituitrin when so treated retained this activity. Again, Meltzer [34] claims there is a difference in action on the enucleated eye between epinephrin and the commercial preparation of pituitary glands. Allers noted that Pituitrin, which is a dilute acetic extract of the glands, gave, like epinephrin, when treated with an alkali, an odor of an alkylamin. Führer [35] has recently stated that B-iminazolylethylamine hydrochloride, or Histamin, when injected intravenously into rabbits, produces the same effects on blood-pressure and the respiration as Pituitrin, but admits it is not the active principle of the pituitary gland, as this substance is more toxic than a corresponding amount of Pituitrin, and while repeated injections of B-iminazolylethylamine will give some tolerance to the injections of the same, yet will not give immunity to Pituitrin, so that at one time Führer suggested that the active principle of the pituitary gland is not B-iminazolylethylamine, but related to it. However, Einis [36] found that the action

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[31] Allers, R., "Zur Kenntniss der wirksamen Substanz in der Hypophysis," *Münch. med. Woch.*, vol. 56, pt. 2, p. 1474 (1909); Houssay, B. A. "Estudios sobre la accion de los extractos hipofisiarios," p. 159.

[32] Meyers, M. K., "Die Wirkung von intravenösen Injektionen von Hypophysenextrakt," *Cent. d. Allg. Path.*, vol. 20, p. 109 (1909); Etienne and Parrisot, *Arch. de méd. Exper.*, July, 1908, found slight lesions.

[33] Cramer, W., "On the Inactivation of Adrenalin *in vitro* and *in vivo*," *Proc. Physiol. Soc.*, p. xxxvi; *Jour. of Physiol.*, vol. 42 (1911).

[34] Meltzer, S. J., "Influence of the Infundibular Portion of the Hypophysis upon the Pupil," *Proc. Soc. Exper. Biol.*, vol. 9, p. 103 (1912). See also Kepinow, p. 261.

[35] Führer, H., "Das Pituitrin und seine wirksamen Bestandteile," *Münch. med. Woch.*, vol. 59, p. 852 (1912); Kaufmann, P., "Ueber den Einfluss der Organextrakte auf die Blutgefässe," *Zeit. f. Physiol.*, vol. 27, p. 532.

[36] Einis, W., "Ueber die Wirkung des Pituitrin und B-imidazolylethylamine auf die Herzaktion," *Biochem. Zeits.*, vol. 52, p. 96.

of B-iminazolylethylamine on the frog heart was different from that of Pituitrin. It is difficult to understand how this substance could be the active pressor constituent of the pituitary glands, because in carnivora it produces a fall in blood-pressure, although it produces a rise in pressure in herbivora, while pituitary extracts cause a rise in rabbits and dogs.[37]

Kepinow has pointed out a synergism between the action of epinephrin and pituitary extracts; that is, small doses of epinephrin are claimed to increase the action of pituitary extracts so that the combined action corresponds to more than their simple addition. Small inactive doses of extracts of the hypophysis increase the action of epinephrin on rabbits; in other words, the animal becomes sensitized.[38]

Chemical Experiments.

Considerable chemical work has been done on the pituitary glands, but apparently no pure pressor compound has as yet been definitely isolated. Calcium, phosphorus, bromine, arsenic, guanin, and cholin have been found to occur in the glands, and, while iodine was suspected, owing to an apparent histological resemblance between the thyreoid and pituitary glands, as yet it has not been proved to be present.

According to our experiments, repeated evaporation of extracts of the pituitary gland, and also putrefaction, will cause rapid diminution in pressor activity. Schaefer and Herring[39] noted that tryptic digestion for 18 hours did not destroy its diuretic or pressor action, and that peptic digestion, while it did not injure its diuretic action, changed the character of the pressor action.

Oliver and Schaefer found that aqueous extracts of pituitary glands could be boiled, at least for a short time, with little or no loss in pressor activity. Aldrich[40] extracted the fresh infundibular portion of the gland with dilute acetic acid and then removed the coag-

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[37] Dale, H. H., and Laidlaw, P. P., "Physiological Action of B-iminazolylethylamine," *Jour. Physiol.*, vol. 41, p. 318 (1910–11).

[38] Kepinow, "Ueber den Synergismus von Hypophysis Extrakt und Adrenalin," *Arch. f. exper. Path.*, vol. 67, p. 247 (1912).

[39] Schaefer and Herring, *l. c.*, p. 22.

[40] Aldrich, T. B., "Preliminary Contribution to the Chemistry of the Infundibular Portion of the Pituitary Body," *Amer. Jour. Phys.* (1907–08), vol. 21, p. xxiii.

ulable proteins by means of heat and filtration. Aqueous extracts of undried pituitaries pass through filter paper with the greatest difficulty, but after thorough coagulation of the proteins the extracts filter readily.

As Lewis, Miller and Matthews showed that a pressor action could be obtained from all portions of the gland, we used the whole gland and avoided the tedious mechanical labor of removing the posterior portion. The fresh beef glands were ground in a meat-chopper and extracted twice with 0.1 per cent. acetic acid, and, after squeezing through cheese-cloth, the extract was coagulated on the water-bath and the filtrate evaporated *in vacuo*. This gradually colored during evaporation and left a brownish-yellow, gummy, non-crystalline mass, which, on intravenous injection into dogs, would induce a marked rise in blood-pressure.*

On treatment with hot methyl alcohol (Merck's highest purity) all the color and activity went into the alcohol. This solution gave a heavy precipitate on the cautious addition of a drop or two of concentrated sulphuric acid, which redissolved with an excess of the acid. This precipitate dissolved in water, forming a reddish solution, and produced a marked rise in blood-pressure. When freshly precipitated it dissolved in hot methyl alcohol or ethyl alcohol (commercial 95 per cent.), but if washed with ether and placed in the desiccator became insoluble in either alcohol. At first we believed this to be a true sulphate mixed with calcium, but found that after further purification it failed to be reprecipitated from methyl alcohol by sulphuric acid, hence we argued that the first precipitation was merely mechanical. This precipitate, dissolved in water, or the acetic-acid extract of the glands, gave a heavy precipitate with lead acetate or lead subacetate, mercuric chloride or uranium acetate.

The filtrate after uranium acetate precipitation was active, but uranium gave no precipitate if the lead precipitation had been completely done. Mercuric chloride also gave a heavy precipitate and the filtrate was active. Gold chloride, platinum chloride, silver acetate, picric acid, picolinic acid, and benzoyl chloride with sodium hydrate, all gave precipitates with a solution of the sulphuric-

* NOTE.—These dogs were narcotized with ether and morphine and the vagi nerves were usually cut. The most satisfactory results were obtained by using young dogs. Older or large ones did not seem to respond well.

acid-alcohol precipitate, or from the acetic acid extract of the glands, but as yet we have been unable to obtain an active pressor compound from any of these precipitates. Aldrich claims to have obtained an active crystalline picrate by precipitation with picric acid from a concentrated solution of the glands purified by precipitation with uranium acetate, but he has published no analyses of this picrate.

We found that sodium tungstate gave an active precipitate which was soluble in acetic acid, but a control solution of sodium tungstate also caused a rise, hence we cannot say whether or not the activity was due to the reagent. We have been unable to throw out an active base by means of alkalies, or any active combination of it by means of aluminum hydroxide, but obtained an amine odor on treatment of active solutions with an alkali. Magnesium oxide seemed to carry down mechanically some of the pressor compound. No active volatile compound was obtained by alkaline distillation.

A marked odor of skatol arose on treating Pituitrin with hydrogen peroxide, and the solution lost its pressor action. Schaefer and Herring state that extracts of the pituitary glands, when treated with this reagent, still induced an increased urinary secretion, but produced merely a slight rise in blood-pressure. In their experiments reducing agents, such as zinc and hydrochloric acid, were without effect, either on the diuretic or on the pressor action of such preparations.

Recently Baudouin [41] claims that he has obtained an ash-free, hygroscopic compound by dissolving the dried acetic acid extract in absolute ethyl alcohol and freezing out the active substance. From methyl alcohol solution of the acetic acid extract we succeeded in freezing out, by means of solid carbon dioxide, an almost white precipitate which caused a marked rise in blood-pressure, and the filtrate was only slightly active, but on resolution of this active precipitate, freezing gave no precipitate.

After precipitating with lead subacetate and removing as much of the lead as possible by phosphoric or sulphuric acid the filtrate was still active, even though hydrogen sulphide was used to remove the last traces of lead; but if hydrogen sulphide alone was used to remove the lead, both the filtrate and precipitate became inactive, but solutions of the glands to which lead had not been added were

[41] Baudouin, A., "Sur le recherche du principe actif de l'hypophyse," *Comp. rend. Soc. de Biol.*, vol. 74, p. 1138 (1913).

uninjured by hydrogen sulphide alone, hence the active pressor compound must have been carried down with the lead sulphide, but as yet we have been unable to recover it from the lead sulphide precipitate. From this precipitation and from the fact that it is completely removed or destroyed by animal charcoal we argued a high molecular weight, although this does not necessarily follow. After thorough precipitation with lead subacetate and freeing from lead with phosphoric acid the filtrate gave no biuret reaction, but gave a reaction with Folin's hydroxy-phenyl reagent. After lead-subacetate precipitation and removal of the lead, neither zinc sulphate nor ammonium sulphate (saturated solution) gave a precipitate.

In connection with one of our students we had begun some work with Caviar pepton * and found that the intravenous injection into a dog of a few milligrams of it would produce a marked and persistent rise in blood-pressure. This at once suggested that there was a pepton which would cause a rise in blood-pressure, or that the rise which followed the injection of Caviar pepton was due to calcium or barium, supposedly used in neutralizing the acid used in the hydrolysis, or to amino-compounds arising in the formation of the pepton, or to albumose, or to some other unknown compound formed along with peptons.

We had noticed that an iodine and potassium iodide solution would produce a precipitate from certain pituitary extracts, and that this precipitate, after decomposing with sulphurous acid, was physiologically active, while Fühner has shown that various active principles were obtained from the phosphotungstic acid precipitate, and Aldrich has obtained an active principle by means of picric acid.

Now certain so-called peptons give precipitates with phosphotungstic acid, iodine and potassium iodide solution and picric acid, and produce an immunity, or rather a tolerance, to a second injection and interfere with coagulation of the blood. Pick and Spiro [42] showed that the depressor action on blood-pressure and the anticoagulant action of Witte's pepton were not due to peptons or albumoses, but to some other compound associated with them; as Pick

* NOTE.—Supplied by the courtesy of the Hoffmann-La Roche Chemical Works of Grenzbach, Germany, through their New York branch.

[42] Pick, E., and Spiro, K., "Ueber gerinnunghemmende Agentien," *Zeits. f. Physiol. Chem.*, vol. 31, p. 235 (1900).

says, "Es gibt Peptone ohne Peptonwirkung und Peptonwirkung ohne Peptone." A number of so-called peptons produce eosinophilia in varying degrees. In some cases of acromegaly, a disease associated with pituitary disturbances, eosinophilia has been reported.[42]

Some pepton preparations induce symptoms similar to those which occur during the anaphylactic reaction. Biedl[43a] claims that Urechia's results with the intraperitoneal injections of pituitary extracts must be interpreted as an anaphylactic reaction, and Pankow[44] found that, after the intravenous injection of 1–5 c.c. of Pituitrin, rabbits became more sensitive to a second injection made in from 1 to 5 days after the first. According to Führer, the respiratory stoppage from Pituitrin resembles that from anaphylaxis.[45] Extracts of the posterior lobe are said to accelerate coagulation of the blood, while those from the anterior lobe retard it.[46] Witte's pepton, especially the portion soluble in absolute alcohol, retards coagulation.[47]

The pituitary gland contains various enzymes, which might form pepton-like bodies.[48]

Paal,[49] by treating albumen with hydrochloric acid, has obtained products which he calls salts of pepton. These, unlike pepton, are soluble in alcohol. Schrötter[50] claims to have obtained similar compounds with albumoses. Peptons consist mainly of mono-amino acids, and, according to De Waele, the pepton action is primarily

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[42] Falta, W., "Die Erkrankungen der Blutdrüsen," 1913, p. 212.

[43a] Biedl, "Innere Sekretion," vol. 2, p. 133 (1913); Urechia, C. J., "Action de l'extrait hypophysaire en injections intrapéritonéales," *Comp. rend. Soc. de Biol.*, vol. 65, p. 278 (1908).

[44] Biedl, *l. c.*, vol. 2, p. 136.

[45] Führer, *l. c.*, p. 406.

[46] Émile-Weil, P., and Boyé, G., "Action différentes des lobes hypophysaires sur la coagulation du sang," *Comp. rend. Soc. de Biol.*, vol. 67, p. 428 (1909).

[47] Zunz, E., "Apropos de l'action anticoagulante des injections intraveineuses de peptone de Witte," *Comp. rend. Soc. de Biol.*, vol. 73, p. 50 (1912).

[48] Buetow, "Zur Kenntniss der Hypophysenzyme," *Biochem. Zeits.*, vol. 54, p. 40 (1913).

[49] Paal, C., "Ueber die Peptonzalze des Eieralbumine," *Ber. d. deutsch. chem. Gesells.*, vol. 27, p. 1845.

[50] Schrötter, *Monats. f. Chemis.*, vol. 14, p. 612 (1893).

an amino action. From Witte's pepton Pick [51] claims to have separated two peptons and four albumoses. However, as Haslam points out, the methods do not give sharp separations.[52] Pick precipitated the primary albumoses by means of ammonium sulphate, and separated them by alcohol; the hetero-albumoses [53] being precipitated by weak ethyl alcohol, while the proto-albumoses remained in solution with rather strong alcohol. The hetero-albumoses would precipitate on dialysis, and long heating converted them into an insoluble compound (dysalbumid). Witte's pepton contained very little of the proto-albumoses. After ammonium sulphate precipitation the filtrate yielded a product which was called albumose C. On treating the hetero-albumoses [54] with hydrochloric acid no tyrosin was obtained, but large amounts of leucin were found, while oxidation with potassium permanganate yielded a compound believed to be phenyl-amino-propionic acid. The proto-albumoses yielded tyrosin and gave a marked skatol odor on decomposition. Pick's hetero-albumose contained no indol nucleus, but yielded large amounts of di-amino compounds.

In one experiment Pick noted that both the proto-albumoses and hetero-albumoses obtained from Witte's pepton caused a rise in blood-pressure, but as these albumoses had been prepared by the ammonium sulphate method the rise may have been due to some of the precipitant, However, another dog merely responded by a fall in blood-pressure when hetero-albumose was injected, and in Popielski's experiments proto-albumose, prepared by Pick's method, produced a rise in blood-pressure in one case, but a fall in the second,[55]

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[51] Pick, E. P., "Zur Kenntniss der peptischen Spaltungsprodukte des Fibrins," *Zeits. f. physiol. Chem.*, vol. 28, p. 219 (1899); *Beitrag z. Chem. Physiol.*, vol. 2, p. 481 (1902). See also Zunz, E., "Die fractionirte Abscheidung der peptischen Verdauungsprodukte mittelst Zinksulfat," *Zeits. f. physiol. Chem.*, vol. 27, p. 219 (1899).

[52] Haslam, H. C., "Separation of Proteins," *Jour. Physiol.*, vol. 36, p. 154 (1907–08).

[53] Kühne and Chittenden.

[54] Schulze, E., "Untersuchungen ueber die Amidosäuren welche bei der Zersetzung der Eiweissstoffe durch Salsäure und durch Barytwasser entstehen," *Zeits. f. physiol. Chem.*, vol. 9, p. 72.

[55] Popielski, L., "Ueber die Wirkungsweise des Chlorbaryium, Adrenalin und Pepton Witte auf den peripherischen vasomotorischen Apparat," *Archiv. f. exper. Path.*, Supplementband 1908, p. 441.

so that Popielski suspected barium to be present in one of the preparations.

Zunz [56] has also found that so-called hetero-albumose, thio-albumose, deutero-albumose, and, especially, proto-albumose produced a rise in blood-pressure in dogs and rabbits. This rise was followed by a marked fall, but, in the case of the proto-albumoses, large amounts were necessary to produce the fall. Witte's pepton has been shown to exert both a vaso-constrictor and a vaso-dilator action.[57] Those products of digestion which gave no biuret test caused a marked fall in blood-pressure. These differences in results may really be due to a difference in the kind of proto-albumose or hetero-albumose used, as we have no positive proof that all fibrin from which Witte's pepton is obtained has necessarily the same chemical composition. Proto-albumose and syn-albumose caused recovery of the exhausted isolated heart, while peptons caused systolic stoppage.

Loeper and Esmonet [58] have found that a weak solution of what is called pepsin caused a slight fall in blood-pressure, followed by a rise. This rise was especially marked if the pepsin was treated with hydrochloric acid, and Popielski [59] noted that a hydrochloric acid preparation of the thymus gland would produce a rise in blood-pressure with a slowed heart, and, like pituitary preparations, produced this rise even after section of the spinal cord. This substance was not precipitated by phosphotungstic acid, lead acetate, or by platinum chloride in alcoholic solution, but was precipitated from absolute alcohol by an absolute alcoholic solution of mercurie chloride.

From this data we argued that some of the pressor activity was due to a compound with high molecular weight; that is, one closely allied to the proteins and which would not dialyse. Schaefer and Herring claimed that the pressor compound of the pituitary would

[56] Zunz, E., "Untersuchungen ueber die Wirkung von Albumosen auf Blutdruck und Atmung," *Archives internat. de Physiol.*, vol. 11, p. 73; "Ueber die Wirkung von Albumosen auf das isolierte ueberlebende Schildkröten Herz," *Ibid.*, vol. 10, p. 200.

[57] Kaufmann, P., "Ueber die Wirkung des Witte-Peptones auf die Blutgefässe," *Zent. f. Physiol.*, vol. 27, p. 724 (1913).

[58] Loeper and Esmonet, "Action vaso-tonique comparée des different produite de sécrétion gastrique," *Comp. rend. Soc. de Biol.*, vol. 70, p. 8 (1911).

[59] Popielski, L., "Ueber eine neue blutdrucksteigernde Substanz des Organismus," *Zent. f. Physiol.*, vol. 23, p. 137 (1909).

dialyse, hence was not a protein. Using toluol as a preservative, we found that much of the color dialysed through heavy parchment paper,* and that this colored solution was usually, though not always, active, while the liquid in the dialyser was intensely active. In this connection it may be remembered that Handovsky and Pick showed that there is in the serum a vaso-constrictor substance which is not dialysable [60] and which is not a globulin.

When our dialysate was collected in fractions, the last fractions were without activity, whereas the fluid within the dialyser was still very active, hence one of the pressor principles, perhaps the mother substance of the dialysable pressor principles, is non-dialysable. The depressor principle passes quickly into the dialysate.

After long dialysis the residue in the dialyser gives a slight precipitate with lead subacetate, none with mercuric acetate or a solution of iodine in potassium iodide, but gives a precipitate with phosphotungstic acid or phospho-molybdic acid and with stannous chloride or mercuric chloride. It also gives a strong biuret reaction.

Führer claims to have separated from pituitary extracts by means of phosphotungstic acid precipitation and subsequent decomposition of the precipitate by means of barium hydrate various pressor compounds. On the other hand, Popielski claims that the pressor activity is in the phosphotungstic acid filtrate.[61] Now it has been found that phosphotungstic acid changes the chemical composition of various compounds,[62] hence there is a possibility that phosphotungstic acid would split our non-dialysable compound into various amines.

The active non-dialysable portion seems to correspond in some respects to the fraction separated by Raper under the name Bα.[63]

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* NOTE.—Animal membranes cannot be used for dialysis, as we have found that the pressor principles are completely removed from the solution by them and cannot be recovered.

[60] Handovsky, H., and Pick, E. P., "Ueber die Entstehung vasokonstriktorischen Substanzen durch Veränderung der Serumkolloide," *Archiv. f. exper. Path.*, vol. 71, p. 62 (1913).

[61] Führer, "Ueber die isolierten wirksamen Substanzen der Hypophysen," *Deutsch. med. Woch.*, vol. 39, p. 491 (1913); Popielski, L., "Hypophysis und ihre Präpärate," *Berl. klin. Woch.*, vol. 50, p. 1156 (1913).

[62] Van Laer, H., "Nature of Amylase," *Bull. Acad. Roy. Belg.*, vol. 4, p. 13; quoted in *Chem. Abstr.*, vol. 8, p. 510 (1914).

[63] Raper, H. S., "Zur Kenntniss der Eiweiss-peptone," *Beitr. z. chem. Physiol.*, vol. 9, p. 168 (1907). See also Stookey, L. B., "Zur Kenntniss der Eiweisspeptone," *Beitr. z. chem. Physiol.*, vol. 7, p. 590 (1906).

A NEW METHOD FOR THE DETERMINATION OF PHENOLPHTHALEIN.

By Dr. A. Mirkin, Cincinnati, O.

Since phenolphthalein has come into extensive use as an ingredient of laxative medicines, frequent occasions arise for its rapid and accurate determination. A few methods have been proposed, but, with the exception of one (*Pharm. Zentrb.*, 1911, p. 1126), they are all gravimetrical, therefore troublesome and unreliable, because applied to an organic substance.

In trying to find a volumetric method for its determination I took advantage of its property to form a well-defined oxime with hydroxylamine. This is the principle of Walker's method for carvone determination, and of Nelson and his estimation of a number of ketones, including camphor.

I first followed closely the directions worked out by the above-mentioned authors, but without result. I then worked according to Friedlander, who first discovered the phenolphthalein oxime, but the results were still far from satisfactory. Finally the following method was discovered, the results of which are very accurate:

1. Gramme phenolphthalein, 0.8 gramme hydroxylamine hydrochloride, and 0.52 gramme 90 per cent. sodium hydroxide solution, finely powdered, are dissolved in 35 to 40 c.c. of absolute alcohol and boiled for two to three hours under a reflex condenser until the liquid turns yellow. The liquid is then diluted with water, transferred to a 250 c.c. volumetric flask, 10 c.c. of 10 per cent. H_2SO_4 are added and the flask filled to the mark with water. 50 C.c. are taken for titration. First the acid is neutralized, using Methyl orange as indicator. Then the excess of hydroxylamine is titrated with N/10KOH, using phenolphthalein as indicator. A blank is run, using the same amounts of hydroxylamine, NaOH and alcohol, and boiled for the same length of time. The difference in the number of cubic centimetres of N/10 alkali used in the titration of the blank experiment and in the sample, multiplied by 316, gives the quantity of phenolphthalein.

When applying the method to medicinal tablets, the tablets were placed in a cylinder and crushed under alcohol with a glass rod. The alcohol was decanted off through a filter into a volumetric flask

and the extraction and decantation continued until complete extraction was obtained. An aliquot part of the extract was then taken for the determination.

The method gives very accurate results in the hands of a careful worker. The yellow color of the oxime does not interfere with the titration, as by proper dilution it colors the liquid only slightly.

Tablets of phenolphthalein frequently contain milk sugar or cane sugar, but as cane sugar does not give an oxime with hydroxylamine, and as milk sugar is practically insoluble in absolute alcohol, they do not interfere with the reaction. In case, however, that the method should give too high a result, it is better to make a volumetric determination of sugar in order to be more sure.

THE ESTIMATION OF MORPHINE IN PILLS, TABLETS, ETC.*

By J. B. Williams.

In a paper read before the last meeting of the Pharmaceutical section of the American Chemical Society Mr. A. D. Thorburn suggests the estimation of morphine in pills, tablets, etc., by making the aqueous solution alkaline and extracting with a mixture of phenyl-ethyl alcohol and benzene, partially evaporating the alkaloidal solution, extracting the residue with N/10 acid and titrating back with N/10 or N/50 alkali, using hæmatoxylin as indicator. This method has recently been tried out with the following results. Duplicate assays of a 2 per cent. solution of morphine sulphate, using 10 c.c. (= 0.2 Gm. morphine sulphate or 0.1506 Gm. anhydrous morphine alkaloid).

A = 0.1827 Gm. morphine sulphate = 91.35 per cent.

B = 0.1919 Gm. morphine sulphate = 95.95 per cent.

The phenyl-ethyl alcohol mixture did not separate sharply even after standing two hours. The morphine is apparently not dissolved in the mixture, but appears to be held in suspension by it. N/50 alkali was used in titration, but the end point with hæmatoxylin as indicator is not sharp or satisfactory.

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* Presented at the meeting of the American Chemical Society at Washington, D. C., December, 1911.

Two further assays of the same solution were made, but after adding the phenyl-ethyl alcohol and benzene mixture and shaking, the separators were allowed to stand over night.

The morphine was precipitated through the liquid and on the sides of the separators. The crystals of morphine were washed off with alcohol and the assay completed. *A*, using cochineal as indicator, gave 0.1872 Gm. morphine sulphate = 93.6 per cent. *B*, with hæmatoxylin as indicator, gave 0.1805 Gm. morphine sulphate = 90.25 per cent. 2 c.c. N/10 acid and 4 or 5 drops of cochineal were added to *B* and again titrated, giving 0.1841 Gm. morphine sulphate = 92.05 per cent.

It was thought that perhaps by replacing the benzene in the phenyl-ethyl alcohol and benzene mixture with benzene or petroleum ether a sharper separation would be obtained. This was tried on a solution of 1 Gm. of morphine alkaloid and 50 c.c. N/10 acid in 100 c.c. Ten cubic centimetres of this solution titrated direct showed the presence of 0.0981 Gm. morphine alkaloid. Ten cubic centimetres extracted by the above modified method, replacing the benzene with petroleum ether, gave a sharp separation but low results, 0.08729 Gm. = 87.29 per cent. being obtained.

Judging from the limited number of assays made, the method is unsatisfactory both as to accuracy, time required, and cost and availability of material.

As above stated, the morphine does not seem to be dissolved in the phenyl-ethyl alcohol and benzene mixture—at least not in the quantity of solvent specified.

The U. S. P. gives the solubility of morphine in alcohol as 1–168 and in chloroform as 1–1800, but in a mixture of these two solvents it will dissolve far more freely than in either of them separately.

In order to ascertain the relative solubility of the freshly-precipitated alkaloid in these solvents, morphine sulphate was added in excess to alcohol, chloroform, and a mixture of alcohol 1 part and chloroform 2 parts, respectively. Sufficient ammonia was added to liberate the alkaloid, and the flasks shaken for two or three hours. Ten cubic centimetres of the filtered liquid were then evaporated to dryness and the alkaloid estimated volumetrically as crystalline morphine. The averages of several estimations, weight to volume, were as follows:

Solvent.	Wt. of cryst. morphine in 10 c.c.	Solubility w-v.
Alcohol	0.0547 Gm.	1–182.6
Chloroform	0.0110 Gm.	1–909
Alcohol 1 / Chloroform 2	0.1316 Gm.	1–76

The solubility of precipitated morphine crystals (dried below 60° C.) in the same solvents was also determined, the average of a number of estimations being:

Solvent.	Wt. of cryst. morphine in 10 c.c.	Solubility w-v.
Alcohol	0.0421 Gm.	1–237.5
Chloroform	0.0025 Gm.	1–4000
Alcohol 1 / Chloroform 2	0.1258 Gm.	1–80

Also the solubility of crystalline morphine in mixtures containing varying proportions of alcohol and chloroform:

Solvent.	Wt. of cryst. morphine in 10 c.c.	Solubility.
Alcohol 1 / Chloroform 1	0.1324 Gm.	1–75.5
Alcohol 1 / Chloroform 2	0.1258 Gm.	1–80
Alcohol 1 / Chloroform 4	0.0879 Gm.	1–114
Alcohol 1 / Chloroform 8	0.512 Gm.	1–195.5

Based on these experiments, the following assay method is recommended:

A number of pills or tablets, or a quantity of the sample for assay containing not more than 0.5 Gm. morphine (preferably from 0.1 to 0.2 Gm.), is dissolved in a few cubic centimetres of acidulated water, either in a separator or in a beaker, and then transferred to a separator, keeping the volume of the liquid as small as possible (from 5 to 10 c.c.); add from 15 to 25 c.c. of mixture of alcohol 1 part and chloroform 2 parts by volume and 2 or 3 c.c. of 10 per cent. solution of ammonia, or sufficient to make distinctly alkaline. Stopper the separator and shake well for 2 or 3 minutes. After separation, which usually takes place inside of a few minutes, draw off the chloroformic solution, filter through cotton, well wet with chloroform, into a wide-mouth flask or beaker of about 150 c.c. capacity. Repeat the extraction with two further like portions of

the alcohol chloroform mixture and then with three 10 c.c. portions of chloroform.

Evaporate the alcohol chloroform solution on a water-bath under a current of warm air to dryness, add a few cubic centimetres of alcohol and again evaporate. Dissolve the residue in an excess of N/10 acid and titrate back with N/50 alkali, using cochineal as indicator. Each cubic centimetre of acid neutralized by the alkaloid = 0.0301 Gm. of crystalline morphine or 0.0376 Gm. morphine sulphate.

Following are some of the results obtained by this method. A 2 per cent. solution of morphine alkaloid was prepared and assayed.

5 c.c. = 0.1 Gm. morphine gave.....	0.0976 Gm. = 97.6 per cent.	
	0.0976 Gm. = 97.6 per cent.	
10 c.c. = 0.2 Gm. morphine gave.....	0.1940 Gm. = 97.0 per cent.	
	0.1952 Gm. = 97.59 per cent.	
20 c.c. = 0.4 Gm. morphine gave.....	0.3901 Gm. = 97.52 per cent.	
	0.3901 Gm. = 97.52 per cent.	

A 2 per cent. solution of commercial morphine sulphate.

5 c.c. = 0.1 Gm. morphine sulphate gave....	0.09944 Gm. = 99.44 per cent.	
	0.09944 Gm. = 99.44 per cent.	
10 c.c = 0.2 Gm. morphine sulphate gave....	0.1981 Gm. = 99.06 per cent.	
	0.1981 Gm. = 99.06 per cent.	
20 c.c. = 0.4 Gm. morphine sulphate gave...	0.3932 Gm. = 98.3 per cent.	
	0.3940 Gm. = 98.5 per cent.	

The quantity of solvent used in the extraction of this sample was the same in each case.

Two weighed quantities of another sample of morphine sulphate 0.0535 and 0.0560 Gm. gave 0.05395 and 0.05634 Gm. respectively when extracted.

A quantity of morphine alkaloid (1 Gm.) was dissolved in exactly 50 c.c. N/10 acid, then made up to 100 c.c. with distilled water; of this solution two 10 c.c. portions were titrated and required for neutralization 8.7 c.c. and 8.7 c.c. of N/50 alkali, showing the presence of 0.09813 Gm. of morphine in each. Two other 10 c.c. portions extracted by the above method, the residue dissolved in 5 c.c. N/10 acid and titrated, required 8.7 c.c. and 8.8 c.c. of N/50 alkali to neutralize, corresponding to 0.09813 Gm. and 0.09752 Gm. respectively.

Several other samples of morphine sulphate and morphine alkaloid gave equally good results. A large number of pills and tablets assayed by this method gave results approximating closely the theoretical content.

The advantages of this method are accuracy, simplicity, and shortness of time required for completion, duplicate assays being easily completed inside of two hours, except when, owing to the presence of sugar or gummy matter in the sample, slight emulsions may form, requiring a little more time for separation, although this can usually be prevented by keeping the aqueous portion to as small a volume as possible.

Since December, 1909, nearly one hundred assays by this method have been made by the writer and so far practically no trouble has been experienced. Of course, this method is available only where the morphine is not combined with other alkaloids, the identity of the alkaloid being taken for granted, but as a check on the manufacture of pills, tablets, etc., it has given good results.

A comparison of results obtained by the two methods follows.

10 C.C. OF A 2 PER CENT. SOLUTION MORPHINE SULPHATE.

By Alcohol-chloroform Method.

I.....0.1984 Gm. morphine sulphate = 99.2 per cent.
II .....0.1976 Gm. morphine sulphate = 98.8 per cent.

By Phenyl-Ethyl Alcohol and Benzene Method.

A ..... = 0.1827 Gm. = 91.35 per cent.
B ..... = 0.1919 Gm. = 95.95 per cent.

The solution containing 1 Gm. morphine alkaloid and 50 c.c. N/10 acid in 100 c.c. gave by direct titration 0.0981 Gm. morphine alkaloid in 10 c.c. and by extraction.

By alcohol-chloroform.	By phenyl-ethyl-alcohol & B. mod.
I..... 0.09812 Gm. = 98.12 per cent.....	= 0.08729 Gm. = 87.29 per cent.
II..... 0.09752 Gm. = 97.52 per cent.....	

Time required for phenyl-ethyl alcohol method, 4 to 7 hours.
Time required for alcohol-chloroform method, 2 to 3 hours.

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BICHLORIDE OF MERCURY TABLETS AND BICHLORIDE TABLET LEGISLATION.[1]

By GEORGE M. BERINGER.

In presenting a paper on such a hackneyed subject as "Bichloride of Mercury Tablets and Bichloride Tablet Legislation," I am well aware that I may be trying your patience on a subject that you may perhaps consider as threadbare. My association with and study of this subject, however, convince me that this is not a dead subject, but contains several problems directly associated with the duties of the druggist and which pharmacists themselves, in a very large measure, must decide.

The extensive use of corrosive sublimate in this form has justified the decision of the Committee of Revision of the U. S. P. to introduce an official formula and by this means to endeavor to formulate additional safeguards to life in their use. The articles that have appeared in the medical, pharmaceutical and lay press, as well as the discussion in the committee, demonstrate that this is a live subject, and associated with it are several questions still to be settled.

In the official recognition of the tablet of mercuric chloride the U. S. P. is only following the example of most of the pharmacopœias that have been revised in recent years. A study of the foreign formulas and a comparison of these and likewise of the commonly used American formulas are interesting.

In American practice, either the Wilson formula containing a mixture of mercuric chloride and ammonium chloride or the Bernay formula containing mercuric chloride and citric acid has been almost exclusively used. In Europe the formula proposed by Angerer for Pastilla Hydrargyri bichlorati has been the type followed. His formula was:

Mercury bichloride,	
Sodium chloride, aa	0.5 Kg.
Eosin	1.0 Gm.

[1] Read before the New Jersey Pharmaceutical Association, Lake Hopatcong, N. J., June 17, 1914.

Mix the salts and color the mixture with the eosin dissolved in water. Allow the mixture to dry in the air and compress into portions weighing 1 or 2 grammes each.

The German Pharmacopœia iv (1900), and again in the fifth edition (1910), adopts the title "Pastilli Hydrargyri bichlorati" and directs that from a mixture of equal parts of mercuric chloride and sodium chloride colored with a red coal-tar dye are to be made cylinders twice as long as thick and weighing 1 or 2 grammes each. Sublimate pastilles must be dispensed in sealed bottles labelled "Poison," and each pastille must be wrapped in black paper on which is printed in white the word "Poison" and the content of mercuric chloride stated in grammes.

The Swedish Pharmacopœia (1901), under the title of Pastilli chlorati hydrargyrici, directed that "Sublimate pastilles" should be hard cylinders or prisms weighing either 1 or 2 grammes each and composed of equal parts of mercuric chloride and sodium chloride and colored red by an aniline dye. It likewise introduced the requirement that each tablet must be wrapped in black paper on which was printed in white the word "*Poison.*"

The Austrian Pharmacopœia (1906), under the title Pastilli hydrargyri bichlorati corrosivi, directed that equal parts of mercuric chloride and sodium chloride should be triturated to a thorough mixture and colored with a solution of eosin and compressed into pastilles weighing 2 grammes or 1 gramme. The pastilles are directed to be dispensed in glass bottles under a poison label, and the pastilles are to be singly wrapped in black paper with the word "Poison" imprinted in white.

The Swiss Pharmacopœia (1907) adopts as a title "Hydrargyrum bichloratum compressum," and as synonym "Pastilli Sublimati." The formula is mercuric chloride 666 Gm., sodium chloride 333 Gm., Eriocyanin A 1 Gm., mixed and compressed into tablets weighing 37.5 cg., 75 cg., and 1.5 Gm., and containing respectively each 25 cg., 50 cg., and 1 Gm. of corrosive sublimate. It directs that each tablet must be wrapped in black paper on which is printed in white the weight of the sublimate contained, the word "Poison," and a death-head design.

The British Pharmaceutical Codex, in the first edition of 1907, and likewise in the 1911 edition, gave formulas for a series of these tablets. Under the name of "Solvellæ Hydrargyri Perchloridi,—Soluble Mercuric Chloride Tablets," and as a synonym "Antiseptic

Perchloride, or Corrosive Sublimate, Tablets," it directed a mixture of equal parts of mercuric chloride and sodium chloride colored with methyl violet to be compressed into tablets containing 8.75 grains of the mercuric chloride, so that one dissolved in the imperial pint (20 fl. ozs.) of water will make a 1/10 per cent. (1 in 1000) solution of mercuric chloride. Under the title " Solvellæ Hydrargyri Perchloridi Fortes or Strong Soluble Mercuric Chloride Tablets," a tablet of the same percentage of essential ingredients, but double the weight, was directed so that one dissolved in 20 fluidounces of water makes 1/5 per cent. (1 in 500) of mercuric chloride. Other formulas are given for a " mild " and for a " small " soluble mercuric chloride tablet yielding, when dissolved as directed, solutions 1 in 4000 and 1 in 4500, the latter being especially recommended as suitable for ophthalmic purposes.

The French Pharmacopœia (1908) presents a new style of formula for use of mercuric chloride in antiseptic solution. Its formula for Papier au Chlorure Mercurique or Charta hydrargyri bichlorati directs that 5 Gm. each of mercuric chloride and sodium chloride be dissolved in a sufficient quantity of distilled water to obtain a volume of 20 c.c. Filter-paper purified by treating with water containing one part of hydrochloric acid to the thousand, washing with pure water and drying, is then saturated with the mercuric chloride solution so that each rectangular surface 5 cm. by 10 cm. shall imbibe 1 c.c. of the solution and represent 25 cg. of mercuric chloride. The superscription, " Corrosive Sublimate " " twenty-five centigrammes," is directed to be printed with indigo carmine, thus producing, when immersed in the proper volume of water, a blue solution. The paper is to be protected from light and moisture and the container to be labelled in indelible red letters " POISON."

These specifications of the Pharmacopée Française, official in that country since July 17, 1908, will yield a product essentially the same as the corrosive sublimate leaflets now being made by an American manufacturer who claims originality and the right to a patent thereon as a new and novel invention.

The Italian Pharmacopœia (1909) gives the title " Pastiglie di Cloruro Mercurico " with the latin *Pastilli bichlorureti hydrargyri.* Its formula is mercuric chloride and sodium chloride equal parts colored with an aqueous solution of eosin and compressed into circular pastilles of 1 or 2 grammes in weight.

It is to be noted that most of the foreign pharmacopœias have simply followed in their titles that proposed by Angerer, and designate these tablets as pastilles. In the same pharmacopœias the title pastilli is frequently applied to mild remedial agents dispensed in the form of confections or lozenges. It is certainly an unfortunate designation and a dangerous classification that would include such a toxic form along with worm lozenges, cough troches, peppermint drops, etc. It is still more to be regretted that it has been proposed to adopt this same title in the U. S. P. IX. The use of the word "pastille" in this connection is not in accordance with the English usage of this word. As defined in the dictionaries the word "pastille" refers to several forms of substances of an entirely different character and dissimilar use.

The Century Dictionary defines pastille or pastil:

"1—A small roll of aromatic paste, composed of gum benzoin, sandalwood, spices, charcoal powder, etc., designed to be burned as a fumigator.

"2—A kind of sugared confection, usually of a strong flavor, of a round flat shape, like peppermint drops.

"3—In art: (*a*) a thin, round cake of water color; (*b*) the method of painting with water colors prepared as pastils or a drawing produced by them.

"4—In pyrotechny a paper case filled with a burning composition intended to cause rotation of a wheel."

Neither of these definitions would cover a mercuric chloride tablet of the shape described and the intended use. In medicine and pharmacy this title had already been preëmpted and used to a considerable extent for medicated confections, and its adoption for such a toxic official preparation is an exceedingly dangerous experiment. It was probably for this reason that the Pharmacopœia Helvetica adopted as its title "Hydrargyrum bichloratum compressum," and the British Pharmaceutical Codex "Solvellæ." The "Solvellæ" of the Codex are compressed tablets or discs intended to be dissolved in water for external or local use. The attempt at classification here made is a step in the right direction. The title coined, however, does not indicate the toxic character and, moreover, is subject to the criticism that it has the appearance of an attempt to imitate the trade-marked name of a certain brand of tablets extensively used in England.

The necessity is for a distinct title that will clearly differentiate

between the medicinal tablets used so extensively for oral administration and such poisonous tablets intended for external use. The safeguarding of life is the first and principal consideration, and this warrants the coining of a new title that shall distinguish the latter as a separate and distinct class. For this purpose I propose *Toxitabellæ* as a distinctive class title, and as the official title for these tablets, " Toxitabellæ Hydrargyri Chloridi Corrosivi," and as the English, " Poison Tablets of Corrosive Mercuric Chloride."

The foreign formulas follow the formula of Angerer in directing equal parts of mercuric chloride and sodium chloride. The American manufacturers generally claim on their labels to adhere to the Wilson formula. Tablets containing the proportion of ammonium chloride directed in this latter formula are prone to change on keeping. They deliquesce in humid atmospheres, and the solubility also deteriorates with age. For these reasons, some of the manufacturers have already substituted sodium chloride for part of the ammonium chloride. One manufacturer advises that he has found preferable a mixture of corrosive sublimate 7.3 parts, ammonium chloride 2.7 parts, sodium chloride 5 parts. The entire replacement of the ammonium chloride by the sodium chloride will doubtless yield a more stable and soluble tablet, and this change should be adopted in the pharmacopœial formula.

The coloring of bichloride of mercury antiseptic tablets was originally proposed not only to make them distinct in color from other tablets of the same shape and size, but the primal idea was to obtain a solution that would have a distinct color and not be mistaken and administered for harmless medications or water. Such accidents had occurred, and to prevent recurrence Angerer proposed as an additional safeguard that the solutions should be colored. It has been difficult to select a red dye that would possess sufficient tinctorial strength so that only a minute quantity would be required and at the same time be permanent and not altered by the action of the chemicals nor fade on keeping. This problem has confronted the manufacturers and has been the subject of considerable experimentation on the part of the writer.

Eosin in the quantity proposed yields a tablet that is distinctly pink, but when in solution (1 $HgCl_2$ in 1000) does not show a distinct color. This practical difficulty with the red dyes, their variable shades, and, moreover, the fact that confections are frequently of this color and liquid medicines are likewise commonly some shade

of red, have led to the use of other colors. The British Pharmaceutical Codex directs methyl violet, which in this combination gives a blue-purple solution. The Swiss Pharmacopœia orders Eriocyanin A, the sodium salt of a sulphonated dye of the triphenylmethane-carbinol type that colors silk and wool a bright blue and is only slightly affected by 10 per cent. hydrochloric acid. The French Codex directs indigo carmine for this purpose.

A number of the manufacturers are already giving preference to the blue tablets. One of these writes: "Green and red colored tablets are not at all satisfactory. I believe that you will agree with me that a sombre blue would prove the most desirable. Confections are made in red, green, yellow, white, and every conceivable color, but the blue is not attractive and therefore would in all probability prove the safest. On the question of coloring for mercuric chloride, Dr. A. G. Rosengarten, whose firm prepares large quantities of mixed salts already colored for the manufacturers, writes me:

"The only satisfactory color that we have found is the blue dye, called indigo carmine. We have not yet found a satisfactory red or green dye, but I can highly recommend indigo carmine for consistent results, and a definite weight of that dye added to a definite weight of corrosive sublimate mixture will produce definite results. I cannot say the same about the other dyes, and I think it will be most desirable to confine the dyes for corrosive sublimate mixture to the one color, blue, and the one dye, indigo carmine."

My own experiments confirm these statements as to the availability of indigo carmine for this purpose. 2.5 mg. per tablet is sufficient to color 500 c.c. of water a distinct blue. If a more intense color be desired, this can be increased up to 5 mg., and the quantity to be specified in the formula for 100 tablets should not exceed .5 Gm. In my experiments with red dyes, iod-eosin and alizarin carmine (sodium alizarin sulphonate) appear to have given the best results with the Wilson type, but the color of the solutions is not as bright a red as might be desired. With the Bernay formula containing citric acid, methyl orange has shown the best results.

The official tablet should be adjusted to the basis of one tablet to 500 c.c. of water, yielding a 1 in 1000 solution, instead of one tablet to the pint, as has been the custom. This will necessitate only a slight increase in the weight.

The shape to be adopted for the official bichloride tablets is one of the questions that is being considered. When these tablets were introduced, the manufacturers quite naturally used the moulds that they had for their compressing machines, and so the unfortunate mistake was made of manufacturing these of the round or disc shape; the same shape and sizes as were used for innocuous medicinal tablets and confections. Fatal accidents have demonstrated that it is imperative that this dangerous practice should be discontinued. Toxic tablets of the bichloride of mercury antiseptic type should be made in a distinct shape that has not been used for any other purpose, and the use of such a shape or form should be restricted by legal enactments to such toxic tablets intended for external use.

In recent years the ingenuity of the American manufacturer has been exercised to obtain a distinctive shape that should characterize and distinguish his brand of "antiseptic tablets." As a result, we now have such shapes as triangular, diamond, square, cube, keystone, clover leaf, exploited as proprietary forms of antiseptic tablets. Every one of these shapes has been commonly used in confections, and their official recognition and continuance for bichloride antiseptic medication would be a repetition of the original fatal error as to the shape of such tablets. The manufacturers of these shapes are each clamoring for the recognition of his particular shape.

The influence of these commercial interests has been exerted to prevent legislative action that would designate an appropriate shape or judicial consideration that would permit judgment to crystallize in favor of an official shape that would insure the greatest amount of protection to life. After all, the question of safety first is the paramount question.

Of all the proposals for a shape for bichloride of mercury tablets, the coffin shape suggested by Mr. F. M. Apple in his paper before the Pennsylvania Pharmaceutical Association seems to be best. This has already been adopted by at least four manufacturers, and its general adoption has only been prevented by the commercial interests back of other designs. Commercial instincts and financial advantages, and not the broad humanitarian principle of what is best to protect life, have been the causes actuating the opposition to legislation and to official recognition of the best suggestion yet offered.

The German Pharmacopœia has been quoted as an authority

to be followed in fixing the U. S. P. standard. I believe that we should appropriate from the foreign pharmacopœias all that our experience and judgment prove to be correct and in accordance with American practice. In this instance I cannot approve of following the dictum of the German Pharmacopœia. I have here a sample of the official German corrosive sublimate tablets that have been in my possession since last March. You will observe, first, that these are not uniform in color and that fading has commenced to take place. Secondly, the shape is in conformity with that of the Ph. Gr., twice as long as broad, and the manufacturer, to show this and possibly to permit of economy in using only half a tablet at a time, has made them with a ridge across the centre. This resembles forms of the pink linked phenolphthalein and other proprietary laxative wafers that are so extensively used in this country. It would be difficult to conceive of a more dangerous experiment than to officially recognize such a shape for bichloride tablets. It would be on a par with the adoption of the Italian pharmacopœial standard of the round tablet which we are now ready to condemn. There is no uniformity in the European pharmacopœias on this formula, and so the argument for adopting an international standard falls flat. Thirdly, the solution, when made of a strength of 1 to 1000, as commonly used, is so delicate a pink tint as to be barely perceptible.

So far as I know, no American manufacturer has yet placed on the market a bichloride of mercury tablet copied after that of the German Pharmacopœia. As this formula has been published for more than fourteen years, this is noteworthy and may be construed as an evidence of the good judgment of our manufacturers. To now insist that the U. S. Pharmacopœia must adopt and make legal a shape that has not met favor in American practice is a unique proposition that lacks the popular approval that is essential to its effectiveness.

The importance of throwing every safeguard possible around the sale and handling of such poisonous substances is now thoroughly recognized. The newspapers have given wide publicity to the deaths, either suicidal or accidental, occurring from bichloride tablets. The evils resulting from the overzealous newspaper which gives its readers all the details of the method by which some poor unfortunate has gone on the long voyage, have been discussed and decried, yet, nevertheless, it continues its course with little or no abatement.

A number of State legislatures in session during the past year have had under consideration acts that would restrict the handling of such poison tablets and define their shape, color, and label, and further prohibit the use of the prescribed shape for any other purpose. There are at least three bills on the same subject now pending in Congress. It is certain that we may expect legislation before long on this entire matter, and it is eminently proper that the drug trade should take an active interest in solving a question of public safety that is so closely associated with our business. Unfortunately, the attitude assumed by some of the druggists is that of thoughtless indifference. The argument advanced by others is that such legislation is only a passing sentimental fad and that it can have no influence on the protection of life. This is so fallacious that it can not long continue to prevent legislation.

It was never expected that any legislation would prevent a person of morbid mind from committing suicide. This is not the purpose of the proposed legislative enactments, but it is contended that in prescribing a distinctive shape for these poison tablets they could under no circumstances be mistaken, either in the day or night, for harmless medications. If a distinctive shape had been supplied the Macon, Ga., banker and the Brooklyn business man, whose deaths beyond question were accidental poisonings, at least these lives could have been spared.

The necessity for a distinctive shape for bichloride of mercury tablets is well shown by the compilation appearing in Public Health Report No. 46, by Martin I. Wilbert, of the United States Public Health Service. In this compilation Mr. Wilbert shows that at that time, in the current price-lists of five leading pharmaceutical manufacturers, there were sixteen different formulas and varying sizes of poison bichloride tablets, five different shapes, five different colors, and only three out of the sixteen were then made of any other shape than the ordinary round tablets used for medicine, such as headache and cold tablets. Could any stronger evidence of the necessity for restrictive legislation and a distinctive shape for these poison tablets be presented than this compilation in a Government bulletin, which shows the present dangerous and unsatisfactory method of marketing these tablets?

The influence of certain manufacturers on proposed legislation is shown in the act passed by the last session of the Maryland legislature. Instead of specifying in the act a distinctive shape or color,

the value of the legislation is largely nullified by the amended form in which the bill was passed. This law provides that " Tablets containing more than 1/10 grain of mercury bichloride must be of either triangular, diamond, square, oblong, or other irregular shape, and their color must be either blue, purple, or green, with the word ' Poison ' imprinted or embossed on each tablet. Further, these tablets can only be sold, dispensed, or given away in bottles upon one side of which the word ' Poison ' has been blown, and when a label with the word ' Poison ' is placed on the face of the bottle."

The restrictions regarding the package and labelling are such as are commonly employed by all of the manufacturers, but the very needed protection to the consumer has been lost sight of by the overpowering commercial spirit that prevented the selection of a distinctive shape for the tablets. Any one of a number of shapes is equivalent to no shape, and the very indefiniteness of the act as passed through the influence of the manufacturers destroys its value as a measure for the safety of the public.

LIQUID PETROLATUM OR " RUSSIAN MINERAL OIL."

REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY.

The following report was submitted to the Council by a referee and publication authorized.

W. A. PUCKNER, *Secretary.*

Petroleum has been in use as a medicine from time immemorial. It was known to Herodotus 400 years before Christ, and is mentioned by Plutarch, Dioscorides, Pliny, and other early writers. It was extensively used by the Arabians and evidently played an important part in the practice of medicine in India, being known to the Bengalese as Muthe Katel. The raw product was the substance used in earlier times and differed much in character and composition, as obtained from different sources.

As an internal remedy it was early employed in chronic pulmonary affections, in obstinate skin diseases, in rheumatism, and for the expelling of tapeworms. It was extensively used for these several purposes in France under the name " Oleum Gabianum " and in North America as " Seneka oil." The internal use of the refined product may be traced to a patent granted to Robert A. Chesebrough,

of New York, in June, 1872, for the manufacture of a "new and useful product from petroleum, named vaseline." This name was originally applied only to a semisolid preparation, but later a liquid product known as liquid vaseline was marketed and for a time exploited as a cure for coughs, colds, consumption, and a number of other diseases and conditions.

The liquid petrolatum has since become known under a variety of names, proprietary and otherwise, in addition to being used as a substitute or an adulterant for other, more costly, fats and oils. Some of the names applied to the product are:

Adepsine oil
Amilee
Atoleine
Atolin
Blandine
Crysmalin
Deeline
Glyco
Glycoline
Glymol
Heavy petroleum oil
Liquid albolene
Liquid cosmoline
Liquid fossiline
Liquid geoline
Liquid paraffin
Liquid petrolatum
Liquid saxoline
Liquid vaseline
Mineral glycerin
Mineral oil
Neutralol
Olo
Paraffin oil
Paroline
Petro
Petrolax
Petrolia
Petrolol
Petronol
Petrosio
Rock oil
Russian liquid petrolatum
Russian mineral oil
Russian paraffin oil
Russol
Saxol
Terralbolia
Terraline
Usoline
Water-white mineral oil
White paraffin oil

A preparation similar to that official in the Pharmacopœia of the United States as liquid petrolatum has been included in many, if not all, of the foreign pharmacopœias, the official title under which this preparation is recognized being as follows:

Petrolatum liquidum, U. S. Pharmacopœia; Paraffinum liquidum, pharmacopœias of Great Britain, Germany, the Netherlands, Japan, Belgium, Austria, Denmark, Switzerland, Sweden, Servia, Italy, Hungary and Russia; Oleum Paraffinæ, Spanish Pharmacopœia; Vaselinum liquidum, French Pharmacopœia, and Oleum vaselini (as a synonym), pharmacopœias of Denmark and Russia.

The requirements of the several pharmacopœias differ somewhat, and the specific gravity as given is as follows:

U. S. P. VIII, 1905	0.870	to 0.940	at 25°
Ph. Brit. IV, 1895	0.885	to 0.890	at 15.5°
B. P. C. II, 1911, usually	0.875	or lower	at 15°
Ph. Germ. V, 1910, at least	0.885		at 15°
Ph. Ross, VI, 1910	0.880	to 0.885	at 15°
Ph. Hung. III, 1909	0.88	to 0.89	at 15°
Ph. Ital. III, 1909	0.875	to 0.890	at 15°
Ph. Fr. V, 1908, about	0.875		at 15°
Ph. Serb. II, 1908, about	0.880		at 15°
Ph. Svec. IX, 1908	0.88	to 0.90	at 15°
Ph. Helv. IV, 1907	0.880	to 0.885	at 15°
Ph. Dan. VII, 1907, at least	0.880		at 15°
Ph. Austr. VIII, 1906, at least	0.880		at 15°
Ph. Belg. III, 1906, not below	0.880		at 15°
Ph. Japon. III, 1906	0.875	to 0.945	at 15°
Ph. Ndl. IV, 1905, not below	0.860		at 15°
Ph. Hisp. VII, 1905	0.840		at 15°

For pharmaceutical purposes, liquid petrolatum may be divided into two grades, the lighter or more limpid oil, used extensively as a vehicle for oil sprays, and the heavier, more viscid oil generally recognized in European pharmacopœias and used as an ingredient of ointments and more recently as a remedy in the treatment of intestinal stasis.

Under petrolatum liquidum the U. S. P. recognizes a mixture of hydrocarbons, chiefly of the methane series, which occurs as a colorless or very slightly yellowish, oily, transparent liquid without odor or taste and having a specific gravity of about 0.870 to 0.940 at 25° C. For the U. S. P. IX, it is proposed to change this requirement somewhat so as to have it apply to a transparent liquid free from fluorescence, without odor or taste and having a specific gravity of from 0.845 to 0.940 at 25° C.

Such a requirement would include all of the available paraffin oils, irrespective of origin. The now commonly available commercial liquid petrolatum, used for pharmaceutical purposes, is practically colorless and all of the better grades are free from odor or taste. The specific gravity varies from 0.855 to 0.895. The lighter oils, having a specific gravity of from 0.860 to 0.870, are usually preferred in the making of oil sprays or solutions of substances to be used as

local applications. The product having a specific gravity above 0.875 evidently contains a considerable amount of dissolved solid paraffin which separates out at temperatures at or below 0° C., but readily dissolves again at temperatures above 10° C.

There is considerable difference in the chemical composition of the paraffin oils obtained from various sources. The American oil consists largely of hydrocarbons of the methane series, while the Russian oil contains naphthenes or hydrocarbons of the benzene series, having the empirical composition of ethylene (C_nH_{2n}), which may be considered as hydrogenated aromatic hydrocarbons, though they behave with reagents very much in the same way as do the hydrocarbons of the methane series.

Mineral oils with a naphthene base are best suited for making white petrolatum, and at the present time the production of the colorless water-white liquid petrolatum appears to be confined largely or almost exclusively to the crude product of the Baku district of Russia, though it is asserted that it is now also made from the Hanover (Germany) crude oil and that some is being produced by "cracking" the white solid paraffin.

It is also said that the American oil can be made water white, but that it is not being so produced at present for economic reasons; the yellowish oil, free from fluorescence, having a very wide sale, both as a lubricant and as a substitute for lard oil and other of the more costly lubricating oils.

From a pharmaceutical point of view it would appear important to note the physical characteristics of the oil and to insist on absence of color, absence of odor and taste, absence of acid and of alkali and a specific gravity in harmony with the purposes for which the oil is to be used.

During the past year or two liquid petrolatum has attracted considerable attention as a remedy in the treatment of intestinal stasis or chronic constipation, the practice of using it having been developed largely through its recommendation by Sir W. Arbuthnot Lane and his associates. This use of liquid petrolatum and of petrolatum products generally is by no means novel. N. A. Randolph,[1] of Philadelphia, was among the first to suggest its use for this purpose in an article published in 1885. Randolph also ap-

[1] Randolph, N. A.: *Therap. Gaz.*, 1885, ix, 732.

pears to have been the first to experiment with petrolatum and to determine its non-absorbability from the intestinal tract. In an article [2] in 1884 he concludes that "pure petrolatum while entirely unirritating to the digestive tract is valueless as a foodstuff."

The experiments recorded by Randolph were evidently prompted by the fact that vaseline and a number of imitation products then on the market were being sold as substitutes for lard and butter, and opinions regarding the food value of petroleum products appear to have differed very materially. Following the experiments of Randolph, Robert Hutchison in 1899 made a series of experiments to demonstrate that petroleum, petrolatum, paraffin and related products were absolutely unassailable by any of the digestive fluids, despite the "large vogue that had of late years been given to various petroleum emulsions, chiefly by ingenious and unterrified advertising." He came to practically the same conclusions arrived at by Randolph fifteen years earlier and pointed out that "liquid paraffin in one sense may be regarded as an artificial intestinal mucus and might in that way have some value on certain forms of constipation."

William Duffield Robinson [3] reports on the use of a perfectly refined colorless and odorless petrolatum, supposedly of American origin. He was able to show that all of the product passed unchanged through the intestinal tract and could be regained from the fæces. In his conclusions he expressed the belief that the effect of the administration of these petroleum products is far more than as a simple intestinal lubricant. In over fifty selected cases in which nutrition, digestion and body-weight were impaired, and the purest oil administered in 1- or 2-dram doses each day for a period of from four to six months, there was in every instance an improvement of weight, health and feeling of well-being. The administration of refined paraffin oil gave no discomfort in any instance, even in cases in which nearly a pint was given in a few hours.

William Ewart [4] suggests liquid paraffin as a safe agent for the local treatment of the lesions in typhoid fever. He says in part: "Mineral oil, such as petrolatum or paraffin, is neither absorbed nor dissolved; therefore, after all absorbable ingestions are taken up by the lacteals, it will still remain in the bowel. In this way pure

[2] Randolph, N. A.: Proc. Acad. Nat. Sc., Philadelphia, 1884, p. 281.
[3] Robinson: William Duffield: *Med. News*, 1900, lxxvii, 56.
[4] Ewart, William: *Brit. Med. Jour.*, 1902, ii, 1505.

liquid paraffin is valuable, precisely because it is inert; moreover, it might some day, perhaps, be made the vehicle for effective topical remedies."

A. D. Schmidt [5] quotes Stubenrath as having given liquid paraffin in the treatment of chronic constipation, and he himself gave as much as 20 gm. of liquid paraffin to adults without observing any injurious effect whatever. He says, "As a result of the administration of liquid paraffin, the fæces are softened considerably and are found under the microscope to contain numerous minute globules of paraffin." He was, however, unable to recover from the fæces the entire quantity of paraffin administered and believes that a certain portion of it, probably the fractions with a low boiling-point, are absorbed or possibly oxidized in the organism.

Maurice Vejux Tyrode [6] also refers to the use of liquid petroleum in the treatment of constipation.

Sir F. Arbuthnot Lane in his recommendations of liquid petrolatum calls it an ideal remedy for stasis, but cautions against the use of the lighter oil as extensively prescribed in this country as a vehicle for sprays in nose and throat work.

Paraffin oil is not absorbed from the alimentary tract and so far as known exerts no deleterious influence. It is usually given in quantities of from 10 to 20 c.c. half an hour or an hour before meals or in larger doses, from 30 to 50 c.c., at one time on retiring. From available evidence it appears that comparatively huge doses may be administered without the production of any untoward results. According to many observers, liquid paraffin should not be given with or after meals because of the inhibiting influence that it may have on the digestion of food. It is not soluble in water or the ordinary solvents and therefore cannot be diluted. The denser oils are preferably slightly warmed or drunk with warm water so as to obviate the disagreeable slimy sensation that persists when taken cold.

Volatile oils may be used in moderate amounts to give a distinctive taste to the otherwise rather insipidly tasteless paraffin oil. Among the more desirable oils to be used for this purpose would be oil of peppermint, oil of cinnamon, oil of betula or methyl salicylate and oil of cloves. From 2 to 10 drops of any of these oils can be added to a pint of the oil. When larger doses of the oil are to be

[5] Schmidt, A. D.: *München. med. Wchnschr.*, 1905, lii, 1907.

[6] Tyrode, Maurice Vejux: *Boston Med. and Surg. Jour.*, 1910, clxii, 673.

given at one time, it would, of course, be advisable to use a comparatively smaller quantity of the volatile oil as a flavor.[7]

From the foregoing it would appear that apart from the Pharmacopœia of the United States, practically all other known pharmacopœias describe a water-white mineral oil under the title "Paraffinum Liquidum" or "Liquid Paraffin" as a colorless, odorless, tasteless, non-fluorescent, oily liquid, free from acids, alkalies and organic impurities. As explained before, the specific gravity of the preparation as recognized in other countries and as offered on the American market at the present time varies considerably, and there appears to be some difference of opinion as to the exact nature of the product that is preferable for use for different purposes. This matter requires further investigation.

Since the definition of liquid petrolatum in the U. S. Pharmacopœia permits the use of fluorescent products of widely varying specific gravities, it is recommended that physicians who desire the water-white non-fluorescent (Russian) mineral oil should use the term "Petrolatum Liquidum, Grave," or "Paraffinum Liquidum, B. P.," if the heavy product recommended by Lane is desired, and "Petrolatum Liquidum, Leve," if the light varieties are required. It is further recommended that under the foregoing names manufacturers and pharmacists be requested to dispense the products, in accordance with the following descriptions:

Petrolatum Liquidum, Grave.—Heavy (Russian) Liquid Petrolatum.—Paraffinum Liquidum, B. P., liquid paraffin.—A transparent, colorless, tasteless, non-fluorescent, oily liquid, odorless when cold but giving off a faint petroleum odor on heating. This prepara-

[7] In addition to the articles referred to in the preceding footnotes, the following are of interest in connection with this subject:

Editorial, *Therap. Gaz.*, 1885, ix, 353.
Junker, F. A.: *Med. Record*, London, 1885, xiii, 506.
Editorial, *Med. News*, 1886, xlviii, 105.
Dunbar: *Deutsch. med. Wchnschr.*, 1896, xxii, 33.
Stubenrath, Franz Casimir: *München. med. Wchnschr.*, 1897, xliv, 639.
London Letter, *Med. News*, 1899, lxxiv, 504.
Hutchison, Robert: *Brit. Med. Jour.*, 1899, i, 724.
Schlesinger, E. G.: *Boston Med. and Surg. Jour.*, 1913, clxix, 14.
Lane, W. Arbuthnot: *Brit. Med. Jour.*, 1913, ii, 1126; Proc. Roy. Soc. Med., 1913, vi, 49; Surg., Gynec. and Obst., 1913, xvi, No. 6.
Jordan, Alfred C.: *Practitioner*, London, February, 1913.
Chrysospathes, J. G.: *Zentralbl. f. Chir.*, 1913, No. 45; abstr., *The Journal A. M. A.*, Dec. 13, 1913, p. 2201.

tion should correspond to the requirements of the British Pharmacopœia for liquid paraffin and have a specific gravity of about 0.885 to 0.890 at 15° C. It is insoluble in water or alcohol, but soluble in boiling absolute alcohol and readily soluble in ether, choloroform, carbon disulphide, petroleum benzin, benzene, and fixed and volatile oils. It serves as a solvent for volatile oils and related substances like camphor, menthol and thymol.

This is the type of preparation used by Sir W. Arbuthnot Lane, and his associates for internal administration. It is also used as a basis for ointments and salves and as a local application to wounds, ulcers and in certain forms of skin diseases in which a simple protective is desired.

Petrolatum Liquidum, Leve.—Light (Russian) Liquid Petrolatum.—A transparent, colorless, tasteless, non-fluorescent, oily liquid, odorless when cold, but giving off a faint petroleum odor on heating. In other respects this preparation should correspond to the pharmacopœial tests for liquid petrolatum and have a specific gravity of about 0.860 to 0.875 at 15° C. Like the heavy variety of liquid petrolatum, it is insoluble in water and alcohol, but soluble in boiling absolute alcohol and readily soluble in ether, chloroform, carbon disulphide, petroleum benzin, benzene and fixed and volatile oils. It serves as a solvent for volatile oils and related substances like camphor, menthol and thymol.

This is a type of preparation extensively used as a vehicle for the oily sprays in nose and throat work. It is also being used as one of the constituents in the now popular paraffin oil cold cream and has been used to some extent for internal administration in the treatment of chronic stasis. Being more limpid than the preparation preferred by Lane, it is more readily taken, though greater care must be exercised in securing a sample devoid of the lighter fractions of petroleum distillates.

PHILADELPHIA COLLEGE OF PHARMACY.

NINETY-THIRD ANNUAL COMMENCEMENT.

The commencement exercises on Thursday, June 18th, brought to a close one of the most successful commencement weeks in the history of the Philadelphia College of Pharmacy. A very large number of the alumni visited the college and attended the various functions. The Baccalaureate services were held at the Church of

St. Luke and the Epiphany, the Rev. David M. Steele delivering an unusually inspiring sermon. On Monday evening the Faculty gave their annual banquet to the graduating class in the College Auditorium. This is always a very interesting occasion, in that it brings together the Faculty and members of the graduating class in a very close relation, enabling them to discuss not only their experiences but some of the larger questions of life.

Tuesday was Alumni Day, the Association holding its annual meeting in the afternoon, and in the evening giving a reception to the members of the graduating class, in addition to the awards of the alumni prizes and a very excellent musical program. Prof. Henry Kraemer gave an address, in which he read the class oration which he had delivered twenty-five years ago, at the time of his graduation from this College. The annual alumni banquet, which was held at the Hotel Walton on Wednesday evening, was very largely attended and was characterized by magnificent alumni and college spirit. The responses by the various representatives of the classes ending in 4's and 9's showed that the movement to mark the centennial of the College and raise $500,000 for new site, new buildings, and additional equipment would receive the hearty coöperation of the alumni.

The commencement on Thursday evening at the Academy of Music marked the climax of the week's celebration. The feature of the evening was the presence of the Governor of Pennsylvania, Hon. John K. Tener, who delivered a brief but very appropriate address to the members of the graduating class and their friends assembled. The opening prayer was made by Rev. W. Quay Rosselle, of Philadelphia, after which the degrees were conferred by President Howard B. French.

The title of Master in Pharmacy (Ph.M.)—In Course—was conferred on Professor Edwin L. Newcomb, P.D., of the University of Minnesota.

The following are the names of those receiving the degree of Doctor in Pharmacy (P.D), together with the subjects of their graduating theses:

Name	Thesis	
Ankrum, Samuel Martin	Acetone	Pennsylvania
Balliet, Woods D.	Serums and Vaccines	Pennsylvania
Berryman, Clarence Haco	The Presence of Arsenic in Tin Foil	New Jersey

Name	Thesis	
Biren, Samuel	Show Card Writing, Advertising and Displaying	Austria
Botdorf, Joseph Franklin	Kaolinum	Pennsylvania
Boyd, William Merton	Improved Methods of Preparing some U. S. P. and N. F. Preparations	Pennsylvania
Burke, John Joseph	Cork: Its Origin and Use	New Jersey
Cahan, Samuel	Sapo Mollis	Russia
Cameron, Ernest Clifford	Production of Cacao	Pennsylvania
Cantner, Paul Clifford	Acidum Hydriodicum Dilutum	Pennsylvania
Carr, Edmund Eugene	Petroselini Fructus	Utah
Coble, Paul Daniel	Ammonium Hypophosphite	Pennsylvania
Cohen, Louis	Pharmacy in Ireland	Pennsylvania
Collins, John Edmund	Sapo Mollis ex Oleo Gossypii Seminis	Pennsylvania
Comber, Gertrude Agnes [P.C.]	Magnesium Oxide	Pennsylvania
Coolbaugh, Leonard Ellsworth	Cudbear	New York
Craft, William Wheeler	The Typho-Bacterins	District of Columbia
Davidson, Wilmer Paul	Tincture of Iodine	Pennsylvania
Dickson, Thomas Young	Ground Flaxseed	Pennsylvania
Dils, Chauncey Lloyd	Manufacture of Window Glass	Pennsylvania
Dougherty, Christ Patrick, Jr.	Aromatic Spirit of Ammonia	Pennsylvania
Duvoisin, Agnes, [P.C.]	Plasters and their Spreading	Pennsylvania
Edwards, Harold Powell	Elixir Ferri, Quininæ et Strychninæ Phosphatum	Maine
Eldredge, William Payson	Phenolsulphonaphthalein: Functional Test—	Pennsylvania
Epstein, Meyer Charles	Chocolate and Cocoa	Pennsylvania
Fiscel, John Arthur	Sapo Mollis	Pennsylvania
Fitzsimmons, William Henry	Crude Petroleum	Pennsylvania
Flanagan, Clark Harrison	Compound Syrup of Hypophosphites, U. S. P.	New York
Fox, James Andrew	Specifications for Portland Cement	Pennsylvania
Frank, William Reuben	Incandescent Gas Lighting	Pennsylvania
Fry, Daniel Joshua, Jr.	Studies of the Origin and Tests of the True Oregon Balsam	Oregon
Gantert, Charles Louis	Mesquite Gum	Pennsylvania
Gehrung, John Clucas	An Accounting System for the Average-Sized Drug Store	Ohio
Gonya, Harry Herome	Calamine	Maine
Gray, John Calvin	Gentian	Pennsylvania
Greene, Barnett Russell	Hydrogen Peroxide, Production Past and Present	Pennsylvania
Griffin, William Harold	Theatrical Cold Cream	New York
Hagenman, Joseph Jeremiah	Diluted Acetic Acid	Pennsylvania

Name	Thesis	
Hall, Jasper Bonsall	Liquor Cresolis Compositus	Maryland
Harris, George Herbert	Paregoric	Pennsylvania
Hayes, John Harry	Modern Industrial Reducing Agents	New York
Heckenberger, William Welcome	The Three Cinnamons	Pennsylvania
Held, Ray Charles	Accurate Weighing	Pennsylvania
Helwig, George L.	Solution of Magnesium Citrate	Pennsylvania
Hinman, Ralph Heber	Glycerophosphates	Pennsylvania
Hurley, William James	Syrup of Quinine	Pennsylvania
Johnson, Clarence Paul	Analysis of Viburnum Opulus	Illinois
Johnson, Ernest Irvin	Medication of Zinc Stearate	Maryland
Kahler, Frank Lot	Eucalyptus	Pennsylvania
Kauffman, Walter Melvin	Structure of Viburnum Opulus and Various Viburnum Barks	Pennsylvania
Kentch, Mortimer Adrian	Medicated Baths and their Extemporaneous Preparation by the Pharmacist	Pennsylvania
Kinbach, Edwin Homer [P.C]	Glass Graduates	Pennsylvania
Kostenbauder, George Henry	The Extemporaneous Preparation of Medical Bougies	Pennsylvania
Krick, Harry Nunemacker	Elixir Terpini Hydratis	Pennsylvania
Kulp, Jacob Harold	The Evils of Newspaper Prescribing	Pennsylvania
LaCourse, Anthony, Jr.	Silicon Carbide	New York
LaWall, Edgar Seiple	Carbon Dioxide in Atmospheric Air and Its Estimation	Pennsylvania
Leidich, Stewart Grier	The Cultivation and Handling of Golden Seal	Pennsylvania
Leinbach, Allen Abraham	Purity of Commercial Gelatin	Pennsylvania
Llewellin, Walter Palmer	Bermuda Arrowroot	Bermuda
Lodge, Roy Paul	The Electrolytic Manufacture of Organic Compounds and Fine Chemicals	New Jersey
McCall, Enzer Lewis	Clay	Pennsylvania
McKean, Harold Andrew [P.C]	The Salt Industry in New York State	New York
McLarren, Chester Lee	Piscidia Erythrina	Pennsylvania
Marshall, Forrest Scott	Tea and Its Caffeine Yield	Pennsylvania
Merz, Elmer Frank	The Phosphates of Calcium	Pennsylvania
Morehead, Robert Crosier	Burgundy Pitch	Virginia
Murtoff, Robert Goulden	Acetylene	Pennsylvania
Myers, Nervin Amos	Bacterins	Pennsylvania
O'Hare, Charles Vincent	Oleum Amygdalæ Amaræ et Benzaldehydum	Kentucky
Owings, Irl Washington	Tablet Making in the Retail Drug Store	Ohio

Name	Thesis	
Pettit, Roland Levi	Face Creams	New Jersey
Rachmell, Nathan	Cottonseed	Pennsylvania
Rogers, Ralph Benjamin	Acacia	New Jersey
Rosenberg, Julius Jacob	Cork	New York
Rosoff, Maurice	Drug Standardization and Its Value in Pharmaceutical Preparations	Pennsylvania
Rowland, Norris Dean	Colorimetric Test for Cubeb	Pennsylvania
Russell, Charles Allen	Potassa Sulphurata	Pennsylvania
Salsbury, Venola Bruce	Emulsion of Cod Liver Oil	Pennsylvania
Schadt, Ralph Monroe	Insecticides	Pennsylvania
Semmel, Irvin Clarence	Prescription Precipitation	Pennsylvania
Shover, Raymond Leslie	Assay of Donovan's Solution	Pennsylvania
Shumaker, Henry Ward	Hygienic Laboratory of the U. S. P. H. Service	Pennsylvania
Slipakoff, Isadore	Sponges	Pennsylvania
Spangler, Edwin Royer	The Rhizome of Asarum Canadense	Pennsylvania
Steever, Ernest Leo	Maple Sap, Syrup and Sugar	Pennsylvania
Stines, George Findley	Carum	Ohio
Sutton, Stanley Eugene	Colloids, their Chemistry and their Practical and Therapeutical Applications	New Jersey
Taylor, Leander Gifford, Jr.	Physiologic Saline Solution	New Jersey
Taylor, William Henry	Logwood	Pennsylvania
Thompson, Frank Davenport	Peroxides and Perborates.	Pennsylvania
Train, Earl Fred	Manna	New York
Trambley, Leo Thomas	The Chemistry of Paper Making.	Pennsylvania
Veigel, Charles Joseph	Volumetric Estimation of Mercury	Pennsylvania
Waker, James Schuteman	Aromatic Fluidextract of Cascara	New Jersey
Watson, John Russell	Camphor: Natural and Synthetic	Pennsylvania
Watson, Walter Irving	Urinalysis	Rhode Island
Way, John Cloud, Jr.	The Contributions of Ancient Greece to Modern Medicine	Pennsylvania
Weinstein, Abram	Hirudo	Pennsylvania
Wheeler, Elwyn J.	Certified Food Colors	N. Hampshire
Whipple, Oscar Kellog, Jr.,	Weeds Used in Official Pharmacy	New Jersey
White, Charles Albert, Jr., [P.C.]	Bee Culture and Its Products Used in Pharmacy	New Jersey
Willmers, Horace William	Sandalwood	Iowa
Wolverton, Fred Cleveland	Podophyllum: Fruit and Its Adjuvant Syrup	Ohio
Wyman, Abraham	Sodium Chloride	Pennsylvania

The following are the names of those graduates who received the degree of Pharmaceutical Chemist [P.C.], together with the subjects of their theses:

Name	Thesis	
Flack, George Thomas	Unfermented Grape Juice, Manufacture and Use	Pennsylvania
Flottman, Charles August	Monazite Sand	Pennsylvania
Hansell, Henry Lewis	Compound Syrup of Hypophosphites (Cloudy)	Pennsylvania
Heinle, Charles Jacob	Paper	Pennsylvania
Hogstad, Anton, Jr.	Belladonna	Wisconsin
Kutteroff, Charles Frederick	Camphor and Its Preparations	New Jersey
Porter, Clarence Frank Turner	Methods for Recovering Volatile and Fixed Oils from Emulsions	Tennessee
Quin, John Frederick Gartner	The Production of Cottonseed Oil	Pennsylvania
Schoonover, Harold Nelson	Buttermilk Cold Cream	Pennsylvania
Wallace, William Romine	The Constituents and Manufacture of Fertilizers	Pennsylvania
Webb, Alvin Chester	Gallæ ex Rhus glabra	New Jersey

Certificates of Proficiency in Chemistry were awarded the following:

Bush, John Lyol	Pennsylvania
Cowles, Henry Carleton, Jr.	Pennsylvania
Hinski, Herman Leo [P.D.]	Pennsylvania
Karns, Harry Clifford, Jr. [P.D.]	Pennsylvania
Kind, Paul Adolph	New Jersey
Tucker, George W.	Pennsylvania

Certificate of Proficiency in the Food and Drug Course:

Clark, Roy Lavender	Utah

Certificates in Bacteriology were awarded the following:

Aguizy, Ahmed Mahmoud El	Egypt
Atkins, John Walter [P.D.]	Pennsylvania
Brown, West Smith [P.D.]	Pennsylvania
Garrett, Joseph Jeffreys	Florida
Hite, Earle Milton	Pennsylvania
Huber, Donald Witherow [P.D.]	Pennsylvania
King, James David [P.D.]	Pennsylvania
Kulp, Jacob Harold	Pennsylvania
Grauss, Gustave Adolph, Jr.	New York
Leathers, Fred. S.	New York
Lemon, Allan	Michigan
Loehle, Frank Aloysius	New York

Linford, Louis George	New York
Merner, Paul Marcus Pfeiffer	Iowa
Patterson, Donald Malcolm	New Jersey
Potterfield, Garland Blair	WestVirginia
Sands, Paul Douglass [P.D.]	Pennsylvania
Shumaker, Henry Ward	Pennsylvania
Smith, John Preston	Pennsylvania
Spangler, Edwin Royer	Pennsylvania
Starr, Miss Mabel	Connecticut
Stein, Joseph	Pennsylvania
Wallace, William Romine	Pennsylvania

Award of Prizes.

The Martin Cup, awarded to the graduation class obtaining a higher average than the one immediately preceding it, was awarded to the class of 1914 and accepted on behalf of the class by their president, Elwyn J. Wheeler, the presentation being made by President French.

The Welcome Cup, awarded to the second year class attaining a higher general average than the preceding class holding it, was awarded to the class of 1915, and was accepted on behalf of the second year class by their president, William R. Tenney, the presentation being made by President French.

"The Graduate 1913" Cup, awarded to the Freshman class for high general record in scholarship, and to be competed for by succeeding Freshman classes, was for the first time presented to the Freshman class of this year and accepted on behalf of the class by their president, Harvey V. Stokely, the presentation being made by Joseph F. Elward, P.D., of the class of 1913.

The grade of distinguished was obtained by Stanley E. Sutton. The following attained the grade of meritorious: W. D. Balliet, L. Cohen, E. S. LaWall, W. R. Wallace, A. C. Webb, A. Weinstein.

The William B. Webb Memorial Prize, a gold medal and certificate, offered for the highest general average in the branches of Committee, Operative Pharmacy and Specimens, was awarded to Stanley E. Sutton, the presentation being made by Joseph L. Lemberger.

The Chemistry Prize, $25, offered by Prof. Samuel P. Sadtler, for knowledge of Quantitative Chemical Analysis, was awarded to William R. Wallace. Edgar S. LaWall received honorable mention in connection therewith.

The Materia Medica Prize, $25, offered by Prof. Clement B. Lowe, for the best examination in Materia Medica and in recog-

nition of Materia Medica Specimens with a meritorious thesis, was awarded to Anton Hogstad, Jr. The following graduates received honorable mention in connection therewith: Woods D. Balliet, Edgar S. LaWall, Elmer F. Merz, Nervin A. Myers, Stanley E. Sutton, Alvin C. Webb and Elwyn J. Wheeler.

The Microscopic Research Prize, a compound microscope, offered by Prof. Henry Kraemer, for the most meritorious thesis involving original microscopic work, was awarded to Anton Hogstad, Jr. The following graduates received honorable mention in connection therewith: Edmund E. Carr, Daniel J. Fry, Jr., William W. Heckenberger, Frank L. Kahler, Walter M. Kauffman, Norris D. Rowland, Edwin R. Spangler and Alvin C. Webb.

The Analytical Chemistry Prize, $25, offered by Prof. Frank X. Moerk, for the best work in qualitative and quantitative analysis, was awarded to William R. Wallace. The following graduates received honorable mention in connection therewith: Stanley E. Sutton and Alvin C. Webb.

The Operative Pharmacy Prize, $20 in gold, offered by Prof. Joseph P. Remington, for the best examination in Operative Pharmacy, was awarded to Stanley E. Sutton. The following graduates received honorable mention in connection therewith: Woods D. Balliet, Charles F. Kutteroff, Forrest S. Marshall, Edwin R. Spangler, Alvin C. Webb and Fred C. Wolverton.

The Maisch Botany Prize, $20 in gold, offered by Mr. Joseph Jacobs, of Atlanta, Ga., was awarded to Alvin C. Webb, the presentation being made by Professor Kraemer. The following graduates received honorable mention in connection therewith: Edmund E. Carr, Daniel J. Fry, Jr., Walter M. Kauffman and Edwin R. Spangler.

The Mahlon N. Kline Theoretical Pharmacy Prize, a Troemner Agate Prescription Balance, for the best examination in Theory and Practice of Pharmacy, was awarded to Stanley E. Sutton, the presentation being made by Joseph W. England.

The Commercial Pharmacy Prize, $20 in gold, offered by Prof. Joseph P. Remington to the graduate who passed the best examination in Commercial Training at the final examination for the degree, was awarded to John C. Gehrung, the presentation being made by Prof. E. Fullerton Cook. The following graduates received honorable mention in connection therewith: Joseph F. Botdorf, Louis Cohen, Meyer C. Epstein, Nervin A. Myers, Stanley E. Sutton, Alvin C. Webb and Elwyn J. Wheeler.

The Instructors' Prize, $20, offered by the Instructors of the College, for the highest term average in the branches of Pharmacy, Chemistry and Materia Medica, was awarded to Stanley E. Sutton, the presentation being made by Prof. F. P. Stroup. The following graduates received honorable mention in connection therewith: Charles L. Gantert, Anthony LaCourse, Jr., Leo T. Trambley, Alvin C. Webb, Abram Weinstein and Elwyn J. Wheeler.

The Pharmacy Quiz Prize, one year's membership in the American Pharmaceutical Association, offered by Prof. Charles H. LaWall, for the best term work in Theory and Practice of Pharmacy, was awarded to Alvin C. Webb. The following graduates received honorable mention in connection therewith: Charles L. Gantert, Stanley E. Sutton, Leo T. Trambley, Abram Weinstein and Elwyn J. Wheeler.

The Special Lecture Report Prize, $10 in gold, awarded for the best written reports of the series of special lectures held under the auspices of the College, session 1913–1914, was awarded to Charles F. Kutteroff, the presentation being made by Dr. A. W. Miller. The following graduates received honorable mention in connection therewith: Louis Cohen, Charles L. Gantert, Anton Hogstad, Jr., and Maurice Rosoff.

The Kappa Psi Fraternity Prize, a gold medal, offered by the Eta Chapter of the Kappa Psi Fraternity to the graduate making the highest general average during the senior year at the College, was awarded to Stanley E. Sutton, the presentation being made by George L. Holstein. The following graduates received honorable mention in connection therewith: Edgar S. LaWall, Alvin C. Webb and Elwyn J. Wheeler.

LEGEND AND SERIAL NUMBER ON INSECTICIDES AND FUNGICIDES ABOLISHED.

THE THREE SECRETARIES FIND THAT GUARANTY LEGEND ON SUBSTANCES USED TO DESTROY OR PREVENT INSECTS AND FUNGI IS DECEPTIVE AND MISLEADING. NO MORE SERIAL NUMBERS TO BE ISSUED OR GUARANTIES ACCEPTED.

Following their action prohibiting the use of a serial number and holding the guaranty legend on foods and drugs, under the Food and Drugs Act, to be deceptive, the Secretaries of the Treasury, Agriculture and Commerce, on June 30, signed an amend-

ment to the regulations under the Insecticide Act abolishing the use of serial numbers on insecticides and fungicides. The amended regulation also holds that the use of the legend "Guaranteed by (name of guarantor) under the Insecticide Act of 1910," on the labelling of insecticides and fungicides, or similar legends is misleading and deceptive in that the public is induced by such legend and serial number to believe that the articles to which they relate have been examined and approved by the Government.

The regulations, therefore, provide that the use of the guaranty legend or any similar legend on labels or packages of insecticides or fungicides, under which are included all substances for destroying or preventing insects or fungi affecting plants and animals, should be discontinued.

The new regulation is to become effective on and after May 1, 1916. In the case of products packed and labelled in accordance with the Insecticide Act and in conformance with the rules and regulations, prior to May 1, 1916, the amendment will become effective on and after November 1, 1916. Manufacturers, however, need not wait until May 1, 1916, to change their labels, but are free to make them conform to the new regulations at any time.

As in the case of the ruling on foods and drugs, the amended regulation as to insecticides and fungicides provide that where a wholesaler, manufacturer or jobber wishes to guarantee his goods so as to protect the dealer from prosecution, he may incorporate this guaranty in or attach it to the bill of sale, invoice, bill of lading, or other schedule. As the protection of the dealer and not a guaranty to the consumer was the original purpose of the legend, the new method fully protects the dealer without misleading the consumer.

In the meantime, the Department notifies the public that the presence of a serial number or guaranty legend on foods and drugs, or on insecticides and fungicides, in no way implies that the Government has tested or approved such articles, or guarantees them to be in compliance with the Federal law.

Office of Information
U. S. Dept. of Agriculture,
Washington, D. C.